Effect of Purified Glucagon (Hyperglycemic-Glycogenolytic Factor, HGF) on Carbohydrate and Corticoid Metabolism in Normal and Diabetic Subjects

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The presence of a substance in commercial insulin which has a blood sugar elevating effect has been known for thirty years. The factor, identified as the hyperglycemic-glycogenolytic factor, should more properly be called "glucagon" since it was first designated as such by Murlin[1] in 1923. Postulated to be a product of the alpha cells of the islets of Langerhans[2], it is carried so precisely through the purification steps used in the commercial preparation of insulin that the richest source of the factor has been commercially available amorphous insulin.

It has been suggested by some investigators that since the exact properties of the material have been so difficult to delineate, it may merely be an artefact, a denatured form of insulin, or a nonspecific substance having an epinephrine-like effect. Others have concluded that the factor is in all probability a hormone[3].

The question of specificity has yet to be answered since a substance having apparently identical properties can be obtained from the gastric mucosa[4]. Cells having some, but not all, of the staining characteristics of pancreatic alpha cells have been found in the gastric mucosa[5], and the two types of cells may be related.

Glucagon can be separated from insulin only with great difficulty. Most of the material previously available for study has been prepared by selective destruction or inactivation of insulin by treatment with either 0.08N potassium hydroxide[4] or with cysteine[6], procedures which leave glucagon relatively unharmed. Some insulin activity could usually be detected, however.

The authors have recently had available for study a highly purified preparation. Utilizing a new method of extraction, glucagon has been isolated by Staub et al[7], of the Lilly Research Laboratories, in crystalline form as illustrated in Figure 1.

Chromatographic analysis has revealed definite differences in the amino acid content of glucagon and insulin. Cysteine, proline and isoleucine are known to be present in insulin and are not found in glucagon. Methionine and tryptophane are both present in glucagon and are not present in insulin. The preparation used in this study was not the crystalline form, although prepared by the same technics and of such purity that one milligram of dry glucagon contained

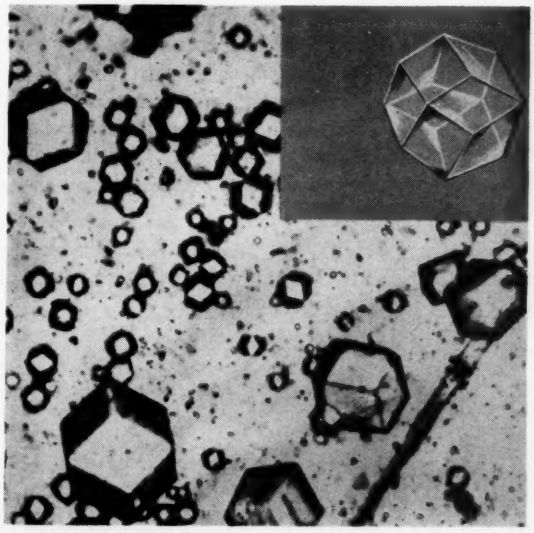

FIGURE 1—Glucagon Crystals. Reproduced courtesy Staub, Sinn and Behrens[7].

From the Lilly Research Laboratories and the Indianapolis General Hospital.

Presented at the Annual Meeting of the American Diabetes Association in New York City on May 31, 1953.

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only 0.005 units of insulin as estimated by animal assay.

Hyperglycemic activity also required stardardization, and the following has been proposed tentatively as a unit. In terms of the biological activity, the unit has been defined as that amount of material per kilogram body weight which, on intravenous administration into a twenty-four-hour fasted, anesthetized (Amobarbital Sodium) cat, produces a blood sugar rise of 30 mg. per 100 cc. within twenty-five minutes[7]. The preparation used in this study assayed at such potency that 0.5 microgram equaled one unit.

Most of the experimental work reported to date has consisted of *in vitro* studies, although several reports on the effect of glucagon on the metabolism of the intact experimental animal and the human are available.

Sutherland and others[3,8,9], utilizing liver slice and liver homogenate technics, have shown that of the three enzymatic reactions involved in the conversion of glycogen to glucose, the limiting one is the phosphorylase reaction which depends upon the ratio of active to inactive phosphorylase. See Figure 2. Glucagon and epinephrine act by accelerating the resynthesis of active phosphorylase, and thereby enhance the production of glucose-1-phosphate. Phosphoglucomutase and phosphatase, necessary for the two additional steps, have been shown to be available in excess or at least in optimal amounts.

Sutherland also has shown that, in contradistinction to epinephrine, intravenous administration of glucagon to the intact animal, although causing as rapid an increase in blood glucose, is not accompanied by a rise in blood lactate, indicating that such a single injection did not influence muscle glycogen.

Myers[10] has shown, by using hepatic vein catheterization, both in animals and in human beings, that hepatic venous glucose concentrations rose more abruptly and more intensely than did peripheral blood glucose values, again confirming earlier work of Collens and Murlin[11] that the site of the hyperglycemic effect was in the liver.

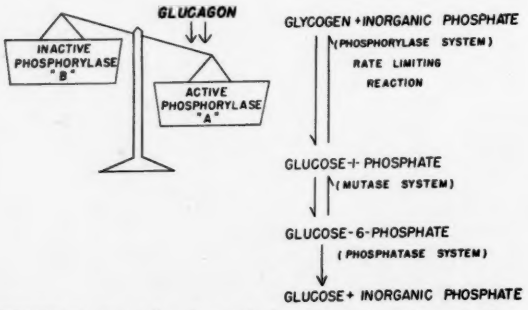

FIGURE 2—Site of action of glucagon. Stimulation of phosphorylase system.

PRESENT STUDY

In an effort to delineate more exactly the effects of glucagon in man, the purified preparation previously described was given intravenously to normal persons and to diabetics of various degrees of severity. All the subjects were eating well, had no complaints and were hospitalized only for the tests. A purely arbitrary dose of 20 units per kilogram weight was selected and utilized throughout the study.

On account of the transient effect of glucagon, an intravenous infusion over a half-hour period was employed to bring out measurable physiological effects which might be too fleeting to be significant using a single injection.

The procedure used was as follows: All subjects were given the substance in the fasting state. The diabetics did not receive insulin on the morning of the test. Glucagon in dosage based upon 20 units per kilogram of body weight was administered over a half-hour period, blood samples were drawn before and at periodic intervals after the infusion, and determinations were made for blood glucose, pyruvate, lactate, inorganic phosphate and potassium. Fractional steroid excretion of urinary 17-hydroxycorticoids and 17-ketosteroids was determined as well as creatinine excretion.

The hepatic glycogenolytic effects of both glucagon and epinephrine have been shown to occur in the same site, that is on the activation of liver phosphorylase and, therefore, it was important to determine differences between the two if such existed. Consequently, several subjects who received glucagon were also given an epinephrine tolerance test. The latter consisted of the intramuscular injection of a 1:1000 solution of epinephrine, dosage being 0.01 cc. per kilogram body weight. Comparative blood determinations were made.

In the normal persons (Figure 3), blood glucose values were at their peak at the termination of the infusion of the glucagon and fell below initial levels between 60 and 90 minutes. The serum inorganic phosphate showed a significant fall with a return towards control levels within 120 minutes. The response of blood glucose and phosphate to epinephrine was consistent with the known effects. The interesting difference was the pyruvate response which rose after epinephrine but failed to rise and, in fact, fell after glucagon.

The typical response to glucagon and epinephrine

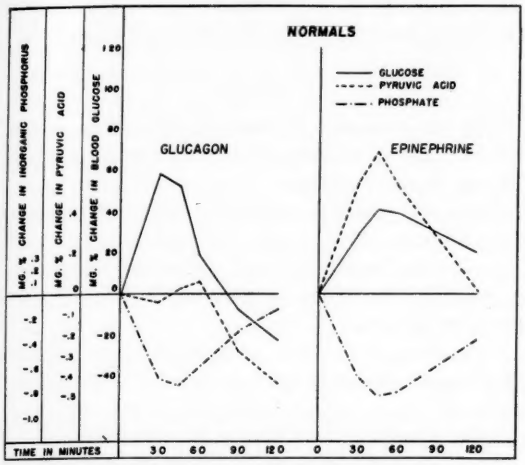

FIGURE 3—Typical glucose and phosphate response in nondiabetic after glucagon and epinephrine.

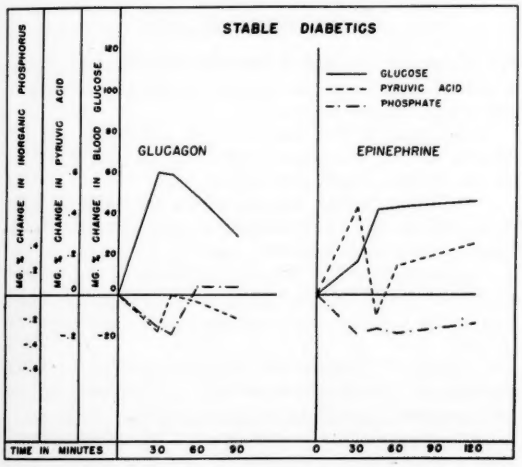

FIGURE 4—Prolonged glucose response and diminished phosphate fall in the stable diabetic.

of the *stable* diabetic is seen in Figure 4. In our classification, these are overweight, middle-aged patients who can tolerate insulin withdrawal and do not develop acidosis readily and whose blood sugar values tend to remain relatively stable throughout the day. Blood glucose values were abnormally elevated after both glucagon and epinephrine. There was a relatively minor fall in blood inorganic phosphorus after both glucagon and epinephrine; and no change in pyruvate occurred after glucagon but elevation did occur after epinephrine.

The most striking differences in response were exhibited in the *unstable* diabetics (Figure 5). These patients are usually, but not always, young, thin diabetics who show a remarkably wide variation in blood sugar when measured four times a day and who display a high degree of insulin sensitivity and are prone to develop acidosis easily.

After glucagon, blood glucose values did not rise as high as in the stable diabetic or normal subject. However, inorganic phosphate fell to levels comparable with the nondiabetic. In the case depicted, there was a rather profound fall in pyruvate. Low pyruvate levels were seen in others of this group, but were not as striking as in this instance. After epinephrine, blood glucose and pyruvate rose to unusually high levels, and inorganic phosphate fell to low levels indicating active phosphorus utilization. Lactate values paralleled pyruvate changes. Potassium changes were inconsistent and probably without definite significance, although there was a tendency for potassium levels to fall in a manner similar to phosphate.

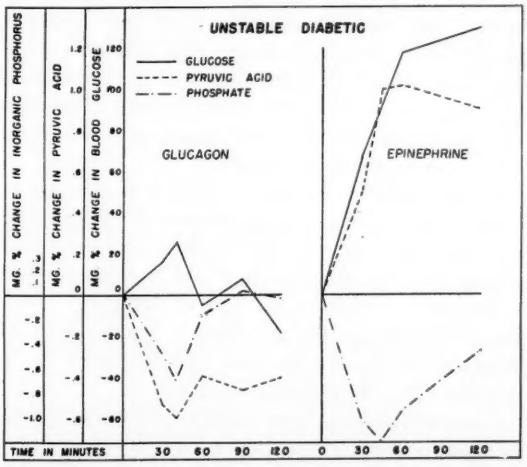

FIGURE 5—Marked response to epinephrine. A "normal" fall in phosphate after glucagon with diminished glucose response.

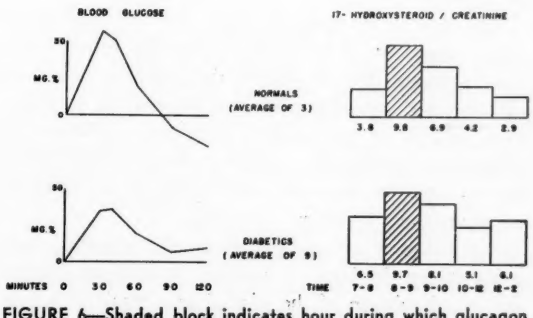

FIGURE 6—Shaded block indicates hour during which glucagon was administered.

The average excretion of urinary steroids of the three normals and the nine diabetics are shown in Figure 6. It would appear that all had some stimulation of steroid excretion during the hour in which glucagon was given. This occurred simultaneously with the hyperglycemic response. These data are based upon hourly 17-hydroxycorticoid/creatinine ratios.

Eosinophile determinations, made before and three hours after the glucagon administration, failed to disclose any consistent pattern of change.

COMMENTS

Different clinical types of diabetes respond differently to glucagon. The height of the glucose response can probably be related to the amount of liver glycogen immediately available. The unstable diabetic, who may be said to have no circulating insulin[12], presumably would have less liver glycogen than the normal as insulin will maintain adequate liver glycogen stores. Therefore, the rise in blood sugar after glucagon would be small. In contrast, the stable diabetic with some circulating insulin may have larger glycogen stores and a greater glucagon response.

If the decline in inorganic phosphate is indicative of carbohydrate utilization, then the unstable diabetic after glucagon can dispose of the hexose derived from liver glycogen to the same degree as the nondiabetic. This is difficult to explain in the light of Bornstein's[12] findings that these patients are deficient in circulating insulin and the known fact that phosphorylation is dependent upon the presence of insulin.

The stable diabetic shows a higher and more prolonged blood glucose elevation and a lesser fall in inorganic phosphate. This may indicate that glucose metabolism is retarded and glycogen mobilized from the liver by glucagon is retained in the blood for a longer period as glucose.

The lack of pyruvate response after glucagon could be accounted for if the hexose phosphate derived from liver glycogen did not follow the complete course of carbohydrate breakdown but was reconverted to glycogen, perhaps in the muscle. These data indicate that glucagon acts primarily upon liver phosphorylase. Elevation of pyruvate after epinephrine can be explained by its glycogenolytic action on muscle.

The enhanced urinary excretion of 17-hydroxycorticoids during the hour of infusion of glucagon may be due to stimulation of the adrenal as a result of a nonspecific stressful situation resulting from the infusion. The possibility of an increased rate of excretion of steroid by the kidney must also be considered.

SUMMARY

The administration of purified glucagon to normal and to diabetic subjects caused an elevation in blood glucose in all individuals.

Stable and unstable diabetics showed differences in their response to glucagon. The stable diabetic had a greater and more prolonged rise in blood sugar and a lesser fall in serum inorganic phosphate than the unstable diabetic.

In contrast to the effects of epinephrine, the infusion of glucagon did not result in an increase in blood pyruvate.

During the hour of glucagon infusion, there was an increase in steroid excretion as shown by determination of the 17-hydroxycorticoid/creatinine ratio.

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DISCUSSION

I. J. PINCUS, M.D. (*Philadelphia*): I think Dr. Kirtley and his collaborators are to be congratulated for this very interesting study which set out to do three things: First, to confirm in the human, findings that had previously been made in experimental animal; this they have succeeded in doing. Secondly, to learn new facts about the physiological effect of this hyperglycemic factor; this, too, they have done. Thirdly, to try to determine what differences there might be between so-called stable and labile diabetics, and here a start has been made.

I should like to comment on many phases of their findings, but shall limit my comment to two. My associates and I are particularly interested in the results that Dr. Kirtley presented on the effect of HGF in regard to the hyperglycemia produced in the labile diabetic. Some years ago we found that these patients showed a large rise in sugar as compared to the normal and the stable diabetic. Our experiments, however, were done under different circumstances, using different preparations, and I think, more importantly, different dietary conditions.

Our patients had been fed and had received their normal morning's insulin before the study was done. It is possible, I believe, that these labile diabetics have a more marked rise, because they rapidly store, then rapidly lose their glycogen stores in the liver. It seems to me possible that more important than the level of liver glycogen is the responsiveness of liver glycogen to HGF, or other factors. It may be that the difference in responsiveness which Dr. Kirtley has discussed is extremely important in explaining some of the phenomena that occur in these patients.

I should like to speak for a moment about the results of the pyruvate determinations. The fact that epinephrine causes a rise and HGF no rise is of considerable interest and shows that the two operate differently on at least some enzyme systems. I should like to suggest the possibility that HGF actually does cause a fall in pyruvate, does act on a muscle enzyme in inhibitory fashion. Some of Dr. Kirtley's results seem too striking to be coincidence, and it is possible he has pointed to another physiological effect of this very interesting substance, which I think can explain some of the discrepancies that occur in clinical diabetes.

The Undernutrition Treatment of Diabetes

In 1916 the whole aspect of diabetes was changed by the revolutionary methods proposed by Frederick M. Allen. It is true that Naunyn and von Noorden had used fasting and vegetable days on occasion, that Guelpa had crudely employed the same and that in this country Hodgson had pointed out the advantages even as early as 1911 of restricted diet in the treatment of diabetes, but the fact remains that it was F. M. Allen who demonstrated on animals and then upon human beings that fasting and undernutrition would give new life to a diabetic, mild, moderate or severe.

I wrote in the preface of my first edition in 1916 "I would not have wished to write a book on diabetes three years ago; today it is a pleasure and an inspiration, because the improvement in treatment is beyond question. The introduction of fasting and emphasis on physical exercise in the treatment of diabetes by Dr. F. M. Allen, of the Rockefeller Institute of Medical Research, has decidedly changed the outlook for this class of patients. "Fasting" is in itself a distinct advance, but the practical simplification of treatment which it entails is an almost greater advantage. Now doctor and patient may know at once whether or not the treatment is successful."

The Allen method brought great alterations. The duration of life went up to 6.1 years, a gain of 25 per cent, and at that time this seemed especially notable. Age at death advanced to 46.7 years and the per cent of those living 20 or more years was changed to 3.1. Still more striking was the fall in deaths due to diabetic coma, from 63.8 per cent to 41.5 per cent, due to the low diet, the administration of small quantities of carbohydrate, liberal amounts of liquids and the prevention of nausea and vomiting largely by the avoidance of alkalies which in their turn we felt formerly blocked the kidneys through excretion of sodium oxybutyrate. Practically no cases of diabetic coma at this period originated in the hospital, a marked contrast to what occurred at the end of the last and the first few days of this century.

From *Diabetes Yesterday, Today, and Tomorrow*, by Elliott P. Joslin, M.D., in Proceedings of the American Diabetes Association, 1:122-123, 1941.

Rapid Estimation of Sugar in Blood or Spinal Fluid with Galatest Reagent

George M. Guest, M.D., and Henri Lestradet, M.D., Cincinnati*

Galatest powder, designed for use as a qualitative test for sugar in urine, is adaptable for quantitative estimations of sugar in low ranges of concentration found in blood and spinal fluid. Such estimations can be made quickly, on 0.1 cc. samples of whole blood or single drops of spinal fluid, with degrees of accuracy quite sufficient for most clinical needs.

Principle: The white Galatest powder, according to the manufacturer's description, is composed of bismuth salt, sodium hydroxide and sodium silicate. When treated with drops of solutions which contain reducing sugar in concentrations from 5 to 40 mg. per 100 cc. it develops colors ranging from yellow to light gray and dark gray. Estimations of the sugar content of blood are made by simultaneously comparing colors developed in the powder by drops of protein-free blood filtrate or clear spinal fluid, appropriately diluted with water, and drops of a series of standard solutions of glucose.

REAGENTS AND APPARATUS

1. Galatest powder, distributed by the Denver Chemical Company, New York. In order to insure a uniform mixture of the powder, empty each newly opened vial into another slightly larger vial equipped with a tightly fitted rubber stopper. Mix by shaking or rotating the vial. In partly emptied original vials the mixing can of course be done without transfer of the powder to a second vial.

2. Standard solutions of glucose in saturated (2 per cent) benzoic acid: 5, 10, 20, 30 and 40 mg. of glucose per 100 cc., prepared by diluting a stock solution of 1 per cent glucose. Keep the solutions in 30 or 50 cc. bottles with dropping pipette and rubber bulb. The pipettes should be selected to deliver drops as nearly uniform as possible. Six bottles (preferably square, for economy of space), including one with distilled water for the control or zero concentration, may be assembled conveniently in a rack, as shown in Figure 1.

3. Pipettes of 0.1 and 0.2 cc. capacity (straight blood sugar pipettes).

4. Tungstic acid protein precipitant, freshly prepared by mixing equal parts of 10 per cent sodium tungstate and 2/3 N sulfuric acid. It is convenient to have each of the two solutions in 50 cc. bottles with pipettes calibrated to deliver 0.2 cc. and rubber bulbs to control the delivery.

5. Vials of 1 or 2 cc. capacity, rubber stoppered, each containing 0.4 cc. of the freshly mixed tungstic acid precipitant.

6. Medicine droppers, with cotton twisted around the tip, to be used as filters. To make the filter moisten the pipette dropper tip slightly (to engage the cotton), then wrap thin wisps of cotton around the tip lightly and tighten by spinning the pipette with one hand while pressing the cotton gently between thumb and finger of the other hand.

7. Pyrex or porcelain plates with 3, 6 or 9 concavities.

8. Testing plates, illustrated in Figure 2 on page 352, designed to facilitate the comparisons of colors. The two charts may be sealed between plastic sheets (Eastman Kodapak, or thin Plexiglass) from which the reagent is easily washed. Or, the tests may be done simply on 4 x 6-inch white cards marked with pencil to indicate the distribution of the standards and dilutions of samples—the cards to be discarded after each test.

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* Fellow of the French Government, under the Fulbright Exchange, in Cincinnati 1949-50.

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FIGURE 1.
Rack with set of six dropper bottles, five with glucose standard solutions and one with water.

PROCEDURE

Deliver 0.1 cc. sample of blood (obtainable by skin prick) into vial containing 0.4 cc. of freshly mixed tungstic acid precipitant: 0.2 cc. of 10 per cent sodium tungstate plus 0.2 cc. 2/3 N sulphuric acid. Stopper, shake and allow to stand 5 minutes for complete precipitation of the proteins. When clear supernatant fluid separates, insert a cotton-tipped medicine dropper into the vial with its bulb squeezed to expel the air, then release the bulb to draw up the filtrate. Withdraw the dropper pipette from the vial, wipe the tip with gauze or soft cellulose paper, removing the cotton tip, and deliver the filtrate (dilution 1:5) into the concavity of a test plate. With a pipette, place 0.2 cc. of water in each of two adjacent concavities. Transfer 0.2 cc. of the 1:5 filtrate to the second concavity, mix with the water, then transfer 0.2 cc. of this 1:10 dilution to the water in the third concavity and mix to make a 1:20 dilution. If the filtrate is scanty, 0.1 cc. portions or even single drops can be used for making the serial dilutions.

On the test plates illustrated in Figure 2, A and B, or on 4 x 6-inch white cards, arrange small piles of Galatest powder in two parallel rows, one of 6 for the standards and one of 3 piles for each sample to be tested. Pour the powder to make conical piles, uniform in size, with bases within circles about 1.2 cm. in diameter. Make a small depression in the powder with the round bottom of a small test tube (1 cm. diameter) or rounded end of a glass rod. If a card is used, mark it with pencil to indicate the distribution of standards and samples to be tested (blood filtrates or spinal fluid), as shown in Figure 2. On each powder in the row for standards place one drop of each solution of glucose: 40, 30, 20, 10 and 5 mg. standards and a drop of water for the zero concentration. On each powder in the row for unknowns place one drop of blood filtrate: 1:5, 1:10 and 1:20 dilutions. Compare and select the colors that most nearly match, with interpolative estimates between the standards where necessary. Tests on clear spinal fluid may be done directly, or after making appropriate dilutions with water (1:2, 1:4 and so on), in concavities of a test plate. Purulent fluids must be deproteinized, as described for blood.

The development of color in the reagent requires heat, developed by the chemical reaction, and is inhibited if the test is done in a cold room or on a cold surface. The test should not be done on glass or porcelain, which conducts heat away rapidly. The amount of powder used should be slightly more than enough to absorb the drop of test solution completely, so that no free liquid is visible when the reaction is complete.

CALCULATION

Concentration of glucose in the standard x dilution of the sample with color most nearly matching = concentration of sugar in the original sample.

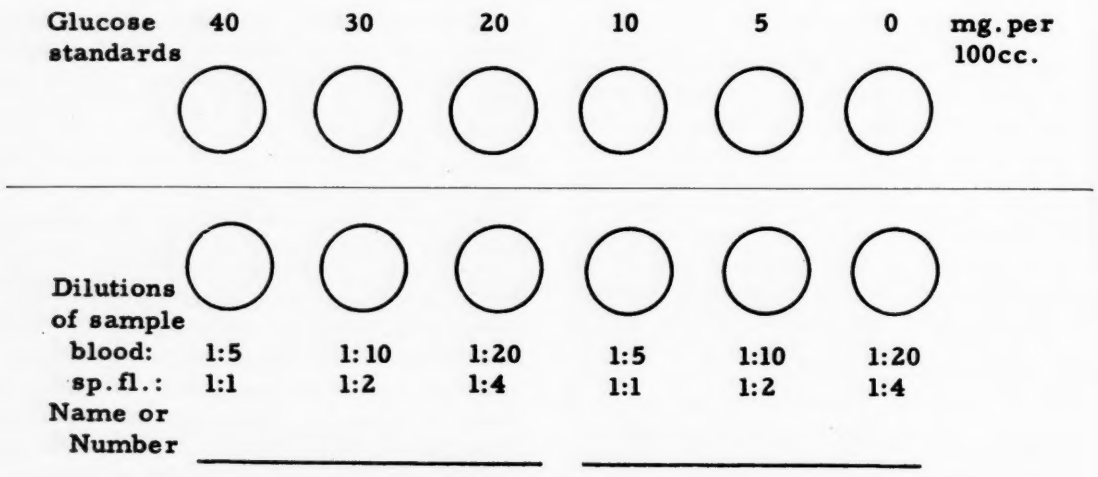
Single tests done with the 1:5 dilution permit estimates of blood sugar within the range from 25, or less, to 200 mg. per 100 cc.; with the 1:10 dilution, estimates within the range 50 to 400 mg. per 100 cc.; and with the 1:20 dilution, 100 to 800 mg. per 100 cc. Tests done on undiluted spinal fluid permit close estimates within the range of the standards, 0 to 40 mg. per 100 cc. Tests done with drops from three dilutions afford confirmatory checks on values in the overlapping ranges and the three values obtained may be averaged.

The method has been subjected to practical tests in several hospitals where comparisons have been made between results obtained by this technic at the bedside and by other standard procedures performed in the

ESTIMATION OF SUGAR IN BLOOD OR SPINAL FLUID

Pour Galatest Powder on the circles in conical piles and make a small concavity in each, using the bottom of a test-tube or rounded end of a glass rod. In the row for standards place on each powder a drop of the glucose solution indicated. In the other row place on each powder a drop of the sample, diluted as indicated (protein-free blood filtrate or clear spinal fluid). Compare and select colors that most nearly match.

CALCULATION: Dilution of sample x concentration of glucose in standard with matching color = concentration of sugar in the original sample.



WARNING: The Galatest powder is caustic. Avoid contact with skin or clothing. Wash into sink with running water.

FIGURE 2. Test plates for comparison of spot tests done with glucose standards and with sample. The upper plate is for glucose standards and lower one for unknown sample. Several plates for samples permit a series of estimations to be made with one row of standards.

laboratories. The results have usually agreed within 10 mg. per 100 cc. in the low ranges from 0 to 50 mg., within 10 to 20 mg. in ranges 50 to 200 mg. and within 50 to 100 mg. in the high ranges above 500 mg. per 100 cc. This degree of accuracy should satisfy nearly all practical clinical needs for following gross fluctuations in blood sugar levels, particularly for following progressive decreases of blood sugar in patients during recovery from diabetic coma, and for the quick recognition of hypoglycemia attending overdosage with insulin. More definitive data gathered in clinical experience will be reported later.

Single drops of the same protein-free blood filtrate, 1:5 dilution, can be used also for rapid estimations of blood ketones, using sodium nitroprusside spot test reagents designed for the detection of ketones in urine. This procedure will be described separately.

SUMMARY

The procedure described, using Galatest reagent (powdered mixture of bismuth salt, sodium hydroxide and sodium silicate) serves as a simple bedside method for the estimation of sugar in 0.1 cc. samples of blood or spinal fluid.

Clinical Value of a Simple Qualitative Test for Plasma Acetone in Diabetic Coma

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On a country-wide basis most patients in diabetic coma are treated by general practitioners. It is not at all to their discredit that, in their broad basis of medical understanding, they may not be familiar with highly technical details in the management of diabetic coma, treatises on which have an unavoidable aura of complexity. One of the objectives of specialists, in my opinion, should be to provide those physicians, who see most patients in diabetic coma, with a plan for diagnosis and therapy which is as simple as a complex subject can be presented and yet has the support of experimental and clinical application under controlled conditions.

To philosophize a moment—is it not true that most writings from specialists are directed to other specialists in the same field and is it not so that specialists are prone to forget that for one patient treated under circumstances oozing with electrolytes, logarithms, and so forth, there are many who must be treated under relatively primitive conditions?

I wish to present an illustration of an attempt to provide for the general practitioner a simple plan which applies in the management of diabetic coma. It provides (a) a means of making an early and differential diagnosis which will permit earlier treatment and the advantages which ensue, (b) a means of appraising the degree of ketosis and hence a guide to initial therapy, (c) indications of returning sensitivity to insulin, which has proved a more reliable clue than any other in our hands, and hence is of value in the prevention of overtherapy and (d) a differentiating indication of significance in the nephropathies and in patients comatose from causes other than ketosis and notably from hypoglycemic reactions.

The pathologic physiology of the development of ketosis is depicted in Figure 1 and the early excretion of ketones in the urine with the later development of excessive ketonemia as the ketosis progresses is illustrated in Figure 2. This relationship of ketonuria and ketonemia is not always maintained in the development of diabetic coma. In unusual cases, the dilution of the urine may account for only grade 3 or even grade 2 reactions for acetone in the urine when grade 4 reactions prevail on testing the plasma. Renal failure may also account for such findings. Because of these exceptions a grade 4 reaction for ketonuria is not considered essential for the diagnosis of diabetic coma. Hence, as illustrated in Figure 3, the clinical picture supported by glycosuria and grade 4 reactions for ketonemia provide the simplest and sure criteria for the diagnosis of diabetic coma. Milder grades of ketonemia—1 and even 2—are seen in disorders characterized by starvation and inadequate intake of carbohydrate, such as from alcoholic bouts, reduction program for the obese, malnutrition and renal disease—usually associated with inadequate intake of food. In none of these disorders have we found grade 4 reactions for ketonemia. To date, this finding is reserved for those patients in diabetic coma.

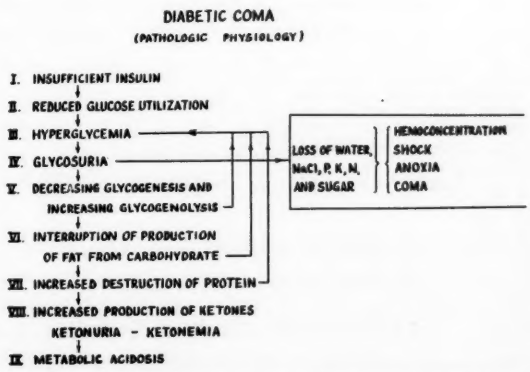

FIGURE 1 Salient features in the development of diabetic coma are presented.

Presented at the Annual Meeting of the American Diabetes Association in New York City on May 31, 1953.

Address communications to Dr. Duncan, Jefferson Medical College, Philadelphia, Pa.

Abnormally great amounts of ketones in the plasma are detectable by means of the Rothera or nitroprusside test. Small increases are not detected by this means. Mary B. Wishart was the first to apply the Rothera test for ketonuria for the detection of ketonemia. Though Miss Wishart never published a paper on the test for acetone in the plasma, her observations have been credited by Allen[1] since 1915. The Rothera-Wishart test* for ketonemia is as follows:

Two drops of plasma, or serum, are placed in a Wassermann tube and supersaturated with ammonium sulphate crystals. Two drops of approximately 5 per cent sodium nitroprusside solution and then two drops of ammonia water are added. The tube is shaken after each addition and then allowed to stand for 3 minutes at the end of which time readings are made—a permanganate (dark purple) color indicating a trace (+), a light blue a moderate reaction (2+) and a deep blue or almost black a heavy reaction for acetone (3+ to 4+).

*The current commercial modifications of this test—the Acetest tablet test and the Denco test—are quite satisfactory.

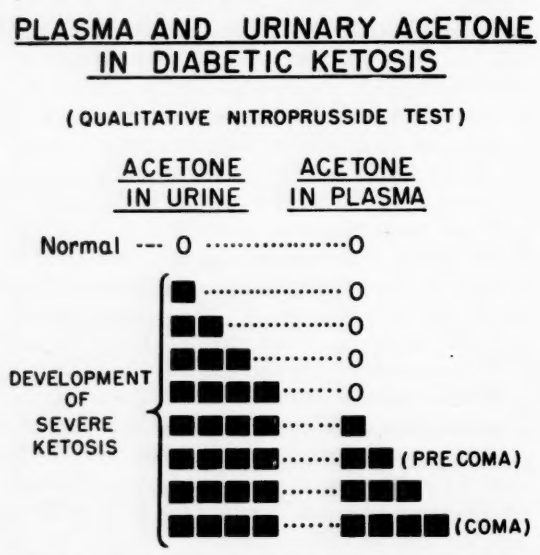

FIGURE 2 The increasing degrees of ketonuria preceding the strong reactions for ketonemia, as usually occur in the development of diabetic coma, are illustrated.

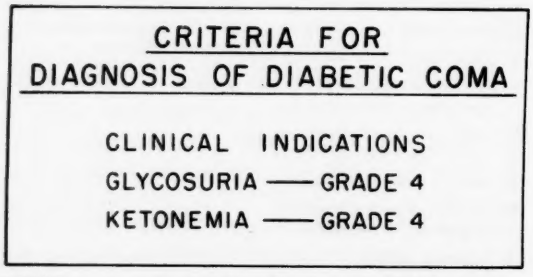

FIGURE 3 A means of making the diagnosis of diabetic coma at the bedside.

EARLY DIAGNOSIS

We have used this test, or modifications of it, since 1926, and on the basis of this experience believe that the detection of glycosuria and a grade 4 reaction for ketonemia in a patient exhibiting clinical evidences of diabetic ketosis affords a reliable diagnosis of diabetic coma. These data are contrasted in 13 consecutive cases of diabetic coma with the usually accepted diagnostic criteria for diabetic coma in Figure 4. Such data obtained at the bedside, in the home, may permit an earlier diagnosis than is usually the case and justify immediate administration of 100 units of unmodified insulin and 4 to 8 ounces of salty broth before moving the patient to the hospital. These data are more readily obtained and often are less subject to error than the carbon

RELATED FINDINGS IN DIAGNOSIS OF DIABETIC COMA

	BLOOD			URINE	
PATIENT	SUGAR	CO_2 meq./L	ACETONE	ACETONE	SUGAR
V.H.	754	5	4+	4+	4+
L.W.	594	0.4	4+	4+	4+
F.M.	270	6.8	4+	4+	4+
H.B.	902	3.6	4+	4+	4+
J.C.	454	6.7	4+	4+	4+
L.V.	470	16	4+	4+	4+
A.B.	450	4	4+	4+	4+
F.P.	332	5.4	4+	4+	4+
H.W.	428	2.3	4+	4+	4+
M.F.	526	17.6	4+	4+	4+
E.D.	1452	5	4+	4+	4+
H.R.	660	9	4+	3+	4+
J.S.	594	8.4	4+	4+	4+

FIGURE 4 Relative chemical values of the blood and urine as found in 13 consecutive cases of clinical diabetic coma, are presented.

dioxide combining power, which may also reflect the effects of features other than ketosis per se, notably renal disease and alkali therapy.

Also, in the puzzling case of coma, diabetic ketosis is excluded by a negative test for excessive ketonemia.

It may be noteworthy that the patient M. F. (Figure 4) did not fulfil the time-honored criteria for diabetic coma, but did satisfy our criteria and proved resistant to insulin, receiving 3200 units in 34 hours without apparent effect. The other patient, L. V. (Figure 4) with a carbon dioxide combining power above that usually considered indicative of coma, is suspected of taking alkali before admission.

THE DEGREE OF KETONEMIA AND THE INITIAL DOSE OF INSULIN

The degree of ketonemia appears to closely parallel the patient's resistance to insulin. Of the several methods of determining the degree of ketonemia we have found a simple dilution method to be satisfactory, clinically, as a crudely quantitative test. Dumm & Shipley[2] have suggested a quantitative method by dilution and Page's[3] observations in this respect support and extend observations reported by us[4].

Our results are illustrated in Figure 5. A grade 4-plus reaction for ketones in the undiluted plasma is followed by diluting a portion of the plasma 1:1 with distilled water or normal saline. A grade 4 reaction on this diluted plasma is followed by testing a further 1:1 dilution. Grade 4 reactions appearing in the undiluted plasma only, indicate a relatively mild ketosis and one which will respond to small amounts of insulin. This is illustrated in Figure 5 by patients H. B. and J. C. If, however, grade 4 reactions are found in the plasma carried to the second dilution the ketosis is of severe degree and much larger doses of insulin are given in the early stages of therapy. See patients V. H. and L. W. Actually, we give, in such cases, 100 units of unmodified insulin for each grade 4 reaction namely undiluted plasma 4-plus—100 units: 50 per cent plasma 4-plus—100 units: 25 per cent plasma 4-plus—100 units: Total 300 units. We have not found grade 4 reactions for ketones in dilutions in which there was less than 25 per cent plasma in the specimen being tested. Subsequent doses are guided more according to the decreasing degree of ketonemia than on the concentration of sugar in the blood.

DEGREE OF KETONEMIA AND INSULIN DOSAGE

PATIENT	BLOOD SUGAR	CO_2 Meq./L	Plasma Acetone				INSULIN REQUIRED IN 1st 12 HRS. (UNITS)
			100%	50%	25%	12.5%	
V.H.	754	5	■■■■	■■■■	■■■■	■■□□	820
L.W.	594	0.4	■■■■	■■■■	■■■■	■■□□	905
H.B.	902	3.6	■■■■	■■■□	Neg.		380
J.C.	454	6.7	■■■■	■■□□	Neg.		160 (24 HRS.)

FIGURE 5 Two patients, V. H. & L. W., in profound diabetic coma as indicated clinically and by grade 4 reactions for ketonemia in the second dilution of plasma and needing large amounts of insulin, are contrasted with H. B. and J. C., who were in relatively mild ketosis as indicated by grade 4 reactions for ketonemia in the undiluted plasma but not in the diluted specimens and by the small amounts of insulin needed to correct the ketosis.

DECREASING KETONEMIA AND RETURNING SENSITIVITY TO INSULIN

These simple dilution tests are of value also in determining the need for insulin during therapy for ketosis. Repetition of the dilution tests for ketonemia, performed at intervals of 2 hours, affords a reliable index of returning sensitivity to insulin. For instance, as grade 4 reactions for ketones disappear from the 25 per cent and then from the 50 per cent plasma solutions, the urgency for insulin decreases and, when less than grade 3 reactions for plasma ketones are found in the undiluted plasma, the amounts and frequency of administration of insulin are sharply reduced. The results of these tests are illustrated in the case of V. H. See Figure 6.

The level of the blood sugar is not used as much as a guide for insulin therapy as it is for reassurance that hyperglycemia is present—a desirable state until the ketosis is corrected. Hyperglycemia of moderate degree, we consider, is highly desirable until the acute phase of the ketosis is corrected. Should the blood sugar decrease below 250 mg. per 100 ml. while severe ketonemia prevails, large doses of insulin would be continued but glucose and fructose therapy would be added—this is an unusual occurrence.

SUMMARY

Our experience with the Rothera-Wishart and similar tests for ketonemia leads us to conclude that it is of special value for the practitioner in making an early and differential diagnosis and instituting early treatment in cases of diabetic coma. It affords a guide to the clinician, in the hospital, in determining the amounts

KETONEMIA AND SENSITIVITY TO INSULIN

(DIABETIC COMA, PATIENT V.H.)

HOURS OF THERAPY	Tests For Plasma Acetone				CO_2	INSULIN UNITS
	100%	50%	25%	12.5%	Meq./L	
0	■■■■	■■■■	■■■■	■■□□	5	250
2	■■■■	■■■■	■■□□	■□□□		150
4	■■■■	■■■□	■□□□	Neg.	12	200
6	■■■□	■■□□	Neg.			200
8	■■■□	■■□□	Neg.		19	20
10	■■□□	■□□□	Neg.			0
12	■□□□	Neg.			19	0
16	Neg.					30
18						0

FIGURE 6 The prompt return of sensitivity to insulin, as the ketonemia decreases to grade 3 reactions in the undiluted plasma, is shown in the treatment of V. H.

of the initial doses of insulin. Also, in indicating returning sensitivity to insulin, it is a guide in the reduction of insulin therapy and hence is of value in reducing the risk of overtreatment with insulin.

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DISCUSSION

LEO P. KRALL, M.D. (*Norfolk, Va.*): It is easy to spend a few minutes discussing something about which one is enthusiastic. It takes much longer to be critical.

We encountered a problem in dealing with merchant seamen who are inclined to minimize their ailments and consequently arrive in the hospital in a severely deteriorated state, often late at night or on Sunday. At these times our regular laboratory staff is absent and the interns on call are requested to do emergency determinations of carbon dioxide combing power and blood sugar. These are done enthusiastically, sometimes inaccurately, often slowly, at a time when speed of treatment is essential.

After Doctor Duncan gave his paper on "Plasma Acetone" at the meeting of the American College of Physicians, in 1952, the use of this test was started by our medical staff. In dealing with patients in severe acidosis we have performed the test hourly and given insulin hourly. Two cases illustrate the results. In the case of a 40-year-old cook, not previously known to have diabetes, admitted in a semicomatose state, with the initial blood sugar 450, recovery occurred in about 14 hours after 990 units of crystalline insulin had been given, guided by plasma acetone readings. A 10-year old boy, known to have diabetes for 6 years, was admitted in classical coma with the carbon dioxide combining power 6.4 mEq./L, the blood sugar 505 and plasma acetone readings 4 plus in all dilutions up to 1 in 8. Using the blood tests to direct treatment, the patient was given 1950 units of crystalline insulin in the first 12 hours. He was able to take nourishment orally in five hours and appeared normal in 14 hours.

We feel that proper charting is important. Only by graphic representation can one keep in mind the dosage of insulin and the effectiveness of previous doses.

There is one danger to keep in mind. The blood acetone test is so easy that inexperienced staff members become casual with their therapy. The treatment of diabetic coma is still a job for people who know what they are doing. The basic principles of treatment are still important. As a guide to treatment, we consider the blood acetone test, properly used, a most useful test.

GEORGE M. GUEST, M.D., (*Cincinnati*): I wish to endorse all that Dr. Duncan and Dr. Krall have said, emphasizing the practical value of simple tests for estimating the level of ketones in blood, to guide the treatment of diabetic acidosis. Numerous investigators have shown that high levels of ketones in the blood of patients in diabetic coma are closely correlated with the severity of acidosis as measured in terms of carbon dioxide content and *p*H of the blood. It is important to note that ketonuria alone does not always afford a satisfactory index of the severity of ketosis, inasmuch as varying degrees of ketonuria and ketonemia may not be closely correlated.

In a patient with good renal function, rapid clearance of ketone bodies from the blood may lead to intense

ketonuria without much accumulation of ketones in the blood, especially in the early stages of development of ketosis. With renal impairment, on the other hand, severe ketonemic acidosis may exist while only traces of ketones are demonstrable in the urine. Under such conditions, in diabetic patients with renal disease, tests for ketones in the blood may afford critical information for the differential diagnosis of ketonemic acidosis, precipitated by a lack of insulin, and of renal acidosis not necessarily associated with a lack of insulin.

The simple test that Dr. Duncan described is far less crude than the title of his paper suggests. The sodium nitroprusside reagents widely used as qualitative tests for ketones in urine are extremely sensitive (namely Acetest Tablets of the Ames Company and Acetone Test Powder of the Denver Chemical Company). But note that in blood the ketone is acetoacetate, not acetone, which produces the purple color with sodium nitroprusside reagents. Little or no acetone exists as such in blood because it is blown off from the lungs as fast as it is formed by the breakdown of acetoacetate. Note, moreover, that the acetoacetate formed in the body and accumulating in the blood gives a color 5 times as intense as that given by an equivalent amount of pure acetone. It is of course the acetoacetate anion, plus betahydroxybutyrate, that contributes to the state of acidosis.

I should like to mention here briefly a method developed in our laboratory with Dr. Lestradet, reported in the graduate course at Toronto in January and soon to be published, whereby the "qualitative" spot test can be made quantitative by the simple procedure of setting up two parallel series of Acetest tablets on which are placed drops of standard solutions of acetone in water (ranging from 6 to 75 mg. per 100 cc.) and drops of plasma or serum diluted serially with water. Colors developed simultaneously on the tablets by single drops of the standard solutions of acetone and drops of diluted serum are compared and colors most nearly matching are selected. For the paired tests, the concentration of acetone in the standard multiplied by the dilution of the sample with matching color, divided by a factor 5.3, gives concentration of acetoacetate in the sample expressed as an equivalent amount of acetone. (The empirical factor of 5.3 was determined by standardization of the procedure with parallel determinations of acetoacetate by the Van Slyke chemical method for determination of acetoacetate.) In severe acidosis, with deep coma, the concentration of betahydroxybutyrate (which does not give a color with the nitroprusside reagent) is usually more than double that of the acetoacetate: thus a rough estimation of total ketones can be made from this test. The determination can be made on a few drops of serum quickly obtainable from small samples of blood drawn by skin puncture and centrifuged in capillary tubes.

EDWARD TOLSTOI, M.D. (*New York City*): I wonder if Doctor Duncan will clarify what he means by coma. To me, it suggests unconsciousness. One of Doctor Duncan's patients, I recall, was able to take some broth, and I am just a little bit confused.

GARFIELD G. DUNCAN, M.D.: I shall be glad to clear up Dr. Tolstoi's confusion. Ordinarily the definition of diabetic coma is—the clinical state notwithstanding—diabetes with the carbon dioxide combining power of the plasma at or below 20 volumes per cent (9 mM./L).

I tried to make it clear that our criteria for the diagnosis of diabetic coma now are more practical, namely the presence of *glycosuria, clinical evidences of ketosis,* and a 4-plus *reaction for plasma acetone.*

I want to thank Doctor Guest for his valuable remarks. He answered very well the question about how the test for plasma acetone should be done.

Mary B. Wishart, who did this test first in 1915, merely applied to the plasma the Rothera test for acetone in the urine. This test thus applied and known as the Rothera-Wishart test is as follows: two drops of plasma or serum are placed in a Wassermann tube and supersaturated with ammonium sulfate crystals; two drops of approximately 5 per cent sodium nitroprusside solution, and then two drops of ammonia water are added. The tube is shaken after each addition and then allowed to stand for three minutes, at the end of this time readings are made. A permanganate color indicates a trace; light blue, 1; a deep blue to almost black, 3 to 4 plus reactions for acetone. That was the basis of the original test, but it is much simpler to use the Acetest tablets manufactured by the Ames Co. A drop of plasma is added to a tablet and the reaction is read against a color chart after a half minute has elapsed. The Denco test using the acetone test powder made by the Denver Chemical Co. is equally satisfactory. Both tests have been used primarily for testing the urine for acetone, but they are just as applicable for testing the plasma.

In regard to the two-hour interval between tests, the selection of this interval is purely arbitrary. Perhaps it would be better to do this test at one-hour intervals, but, two-hour intervals have been satisfactory.

Pharmacologic and Clinical Studies on Two New Types of Long-Acting Insulins with Special Reference to Zinc Insulin Preparations (Novo): A Preliminary Report

Joseph L. Izzo, M.D. with the assistance of Alfreda M. Gabiga, B.S., and Joanne Hoffmaster, B.S. Rochester, New York

Hallas-Moller and his co-workers have reported from Denmark recently the following observations concerning zinc-insulin suspensions.[1-5]

1. In suitable concentration and buffering media zinc ions can bind insulin at the *p*H of the blood to form insoluble zinc-insulin compounds without the presence of modifying agents such as protamine, globin, and so forth, provided that interfering substances such as phosphate and citrate are not present. (2) Such zinc-insulin suspensions show a prolonged insulin effect in biological experiments, the range of activity being dependent mainly upon the physical state of the precipitated insulin—amorphous or crystalline (size and shape of crystals). (3) Clinical experiments on diabetics have confirmed that zinc-insulin suspensions can be prepared with different ranges of activity suitable for clinical use.

We are presenting a preliminary report of adjunct studies on the timing of such preparations in collaboration with the Lilly Research Laboratories where these preparations are under investigation. A long-acting zinc-insulin preparation* somewhat similar to the novo preparation designated as "Ultralente" and bearing the lot No. 2958 has been compared with NPH insulin in respect to: (1) Solubility properties in serum; (2) daily pattern of distribution of insulin activity in patients with unstable diabetes; (3) behavior in patients followed in the clinic under routine conditions. A second new type of preparation, Special Insulin (190-4B-111), a clear acid solution of chemically modified insulin also has been compared.

EXPERIMENTAL DESIGN

1. *Comparison of solubility properties in serum.* The solubility properties of NPH insulin and Insulin 2958 were compared in 60 per cent pooled human sera at *p*H 7.4 and 37 degrees C. according to a method described previously[6]. It was shown[6] that while suspensions of long-acting insulins are not soluble in water they are soluble in serum, the rate and extent varying in a characteristic fashion with the particular type. The high correlation between the solubility curve and relative clinical timing of a given preparation [6, 7] suggest that the timing of such a preparation is a direct function of its solubility properties. In fact, on the basis of cumulative experience, it is possible to predict the approximate relative timing of a given preparation from its solubility curve alone.

2. *Comparison of daily patterns of distribution of insulin activity in patients with unstable diabetes.* The method has been described in detail elsewhere[8]. Briefly, the procedure was as follows: Four patients (two males and two females) with severe unstable diabetes lived quietly on the metabolic floor under routine but controlled conditions throughout the period of investigation. *Only patients with the unstable form of diabetes were chosen because previous studies*[8-11] *have shown that*

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Supported by a research grant from Eli Lilly and Company.

Presented at the 13th annual meeting of the American Diabetes Association, New York City, May 31, 1953.

Address communications to Doctor Izzo, Department of Medicine, University of Rochester, School of Medicine.

*This preparation will hereafter be referred to simply as Insulin 2958.

significant differences in insulin timing are discernible only in the relatively unstable groups of diabetics. Differences in timing tend to be minimized in the *relatively stable group* and accentuated in the *relatively unstable group.* Each patient was maintained on a constant weighed diet of identical foods and food values considered to be appropriate for the particular individual (Table 1). Each of the three insulins, NPH, 2958 and 190-4B-111, were compared in each of three patients (M.K., H.S. and G.C.). In the fourth patient (H.W.) only Insulins NPH and 2958 were compared.

TABLE 1
Supplementary information about the diets of the patients in this study

Patient	Age	Sex	Meals				
			Time	Protein (in g.)	Fat (in g.)	Carbohydrate (in g.)	Calories
H.S.	68	F	8 AM	18.9	23.1	46.7	
			12 Noon	37.1	33.9	77.0	
			3 PM	7.0	0.2	10.2	
			5 PM	23.2	25.8	77.3	
			9:30 PM	8.2	9.3	18.2	
			Totals	94.4	92.3	229.4	2126
M.K.	34	M	8 AM	28.7	75.0	67.5	
			12 Noon	31.8	34.9	74.6	
			3 PM	7.7	8.5	10.8	
			5 PM	23.2	23.9	73.5	
			9:30 PM	8.0	8.8	21.7	
			Totals	99.4	151.1	248.1	2750
G.C.	54	F	8 AM	15.2	8.0	31.8	
			12 Noon	25.9	23.2	45.7	
			3 PM	0.5	0.2	10.1	
			5 PM	23.7	18.6	45.2	
			9:30 PM	4.6	0.2	14.5	
			Totals	69.9	50.2	147.3	1321
H.W.	76	M	8 AM	21.0	30.0	48.2	
			12 Noon	28.4	24.3	61.2	
			5 PM	30.1	20.0	58.8	
			9:30 PM	8.5	3.4	18.4	
			Totals	88.0	77.7	186.6	1798

The comparisons were based on the blood and urinary sugar responses to single daily doses of the given insulin over periods of four to seven consecutive days. On changing from one insulin to another a period of adjustment (two to three days) was allowed before the comparison was made. Changes in tolerance necessitated slight adjustments in dose from time to time. Blood sugars were determined[9] four times daily at 8:00 a.m., 11:30 a.m., 4:30 p.m. and 9:30 p.m. Twenty-four-hour urines were collected in four periods: 7:30-11:30 a.m., 11:30-4:30 p.m., 4:30-9:30 p.m. and 9:30-7:30 a.m., and analyzed quantitatively for sugar[10].

3. *Comparative behavior in patients followed in the clinic under routine conditions.* The clinical timing of Insulins NPH, 2958 and 190-4B-111 was compared over periods of several weeks in each of 13 patients with unstable and eight patients with stable diabetes followed periodically in the clinic under their routine conditions of life. While this method is not quantitative and is much less sensitive than the two just described it serves to corroborate and confirm their clinical significance.

ANALYSIS OF THE DATA

1. The solubility curves of Insulins NPH and 2958 are shown in Figure 1. For comparative purposes the solubility curve of standard protamine zinc insulin obtained from previous data has also been included. The values plotted are averages of duplicate runs in three different batches of pooled sera performed at three different times. Definite and characteristic differences in the solubility curves of Insulin NPH and 2958 can be

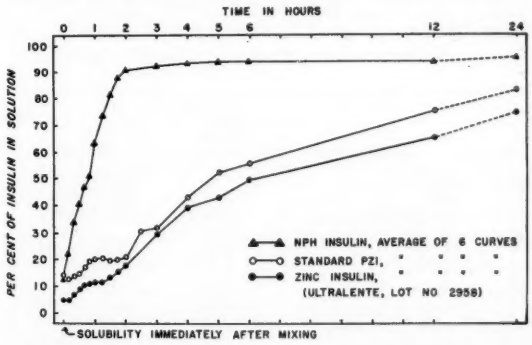
TIME IN HOURS
0 1 2 3 4 5 6 12 24
100 90 80 70 60 50 40 30 20 10 0
PER CENT OF INSULIN IN SOLUTION
NPH INSULIN, AVERAGE OF 6 CURVES
STANDARD PZI, " " " "
ZINC INSULIN, " " " "
(ULTRALENTE, LOT NO 2958)
SOLUBILITY IMMEDIATELY AFTER MIXING

FIGURE 1. Solubility curves of three different types of modified insulin in 60 per cent pooled human sera at 37°C. and pH 7.3.

noted. Insulin 2958 dissolved at a definitely slower rate than NPH insulin. The latter proceeded into solution at a steady rate and by the fifth hour was practically all dissolved. In contrast, Insulin 2958 began to dissolve much more slowly, less than 50 per cent being in solution by the end of the fifth hour and only 75 per cent in solution at the end of 24 hours. It is of interest that the solubility properties of Insulin 2958 and standard PZI are much alike. Note the proximity and similarity in contour of the two curves (Figure 1). However, one important difference in the solubility properties of Insulin 2958 and PZI is that the individual curves (not shown here) of the former are more consistent and uniform than those of the latter.

Comparative solubility properties of Insulin 190-4B-111 could not be studied in the same manner because it is already in solution. Interestingly enough, when the

*p*H of solution was adjusted to that of the body tissues no appreciable precipitate formed. Upon mixing Insulin 190-4B-111 with 60 per cent pooled human sera at *p*H 7.4 and 37 degrees C. only a slight precipitate formed, most of which cleared in a matter of minutes.

2. The blood and urinary sugar data of the four unstable diabetics studied are summarized in Tables 2 and 3. The effect of the insulins on the variability of the blood and urinary sugar responses has been used as the basis of comparison. For a full description of this method of analysis, the principles involved, basic differences from all other methods of comparison and precise definitions of the different components of variability measured refer to previous publications [8, 11]. The total variability among the blood or urinary sugar responses for each patient on each insulin has been divided into two components, intra- and inter-daily variability. It was shown in a larger study[8] that different modified insulins displayed no differential ability to control the extent of intra- and inter-daily variability of the blood or urinary sugar responses. On the other hand, type of insulin did influence the pattern of intra-daily variability but only in the unstable group. Consequently, this analysis includes only a comparison of the effect of the insulins on the pattern of the intra-daily variability, or, in other words, the daily pattern of distribution of insulin activity. In order to describe the pattern of intra-daily variability the deviations from the *daily mean* blood sugar* at the four specified times of the day have been calculated for each patient on each insulin. Figures 2—5 illustrate graphically the daily patterns over periods of

*The deviations have also been calculated for the urinary sugar determinations. Since they reflect the same patterns as the blood sugars, they are not presented.

TABLE II

Summary of blood sugar data

Patient	Insulin Type	Average Daily Dose (Units)	Mean and Range of Blood Sugar in mg. % at				Number of Days of Observation
			8:00 A.M.	11:30 A.M.	4:30 P.M.	9:30 P.M.	
M.K.	NPH	40	145(105-210)	186(125-302)	258(149-353)	322(256-368)	4
	2958	41.7	253(100-377)	357(182-472)	445(273-524)	460(305-532)	7
	190-4B-111	44.5	366(268-442)	337(235-430)	338(290-392)	404(318-500)	4
H.W.	NPH	50	240(160-350)	276(255-293)	294(277-314)	304(186-378)	3
	2958	52.5	282(67-462)	398(196-504)	366(109-467)	425(244-497)	4
H.S.	2958	76	61(55- 66)	221(199-249)	302(204-321)	297(265-329)	4
	NPH (Commercial)	72	196(95-289)	220(111-317)	136(44-232)	174(83-231)	4
	NPH Ax7147-A	66	56(46- 73)	161(132-198)	165(90-221)	177(103-249)	4
	190-4B-111	62	370(361-407)	219(200-237)	302(232-357)	381(368-437)	4
G.C.	NPH	53	262(189-326)	311(284-331)	290(268-307)	280(209-382)	4
	2958	60	183(130-288)	283(237-340)	315(274-362)	286(261-307)	4
	190-4B-111	46	291(264-305)	275(223-302)	133(99-170)	184(95-260)	4

TABLE III

Summary of urinary sugar data

Patient	Insulin Type	Average Daily Dose (Units)	Mean and Range of Urinary Sugar in G. From					No. of Days of Observation
			8:00 A.M.-12 Noon	12 Noon-5:00 P.M.	5 P.M.-9:30 P.M.	9:30 P.M.-8:00 A.M.	Daily Total	
M.K.	NPH-Ax7147-A	40	2.17(0.42- 5.74)	7.33(0.56-20.30)	15.41(0.29-33.60)	6.93(0.19-11.45)	25.91(1.39- 71.09)	4
	2958	41.7	11.21(0.99-19.45)	27.10(7.10-52.50)	49.26(34.90-58.40)	48.07(42.70-63.40)	120.91(12.21-169.30)	7
	190-4B-111	44.5	12.72(4.12-24.09)	12.55(1.60-28.01)	24.84(14.45-39.30)	56.48(15.21-88.50)	109.09(43.87-174.20)	4
H.W.	NPH	No data						
	2958							
H.S.	2958	76	1.80(0.99- 2.95)	19.49(15.35-22.20)	26.17(19.10-37.99)	7.13(4.23-12.10)	54.59(42.24- 65.01)	4
	NPH (Commer.)	72	8.81(1.58-17.40)	6.70(0.30-18.70)	4.24(0.14- 9.35)	3.38(0.74- 9.25)	23.13(3.86- 43.05)	4
	NPH-Ax7147-A	66	1.59(0.66- 2.34)	1.89(0.51- 2.50)	5.45(1.71- 9.59)	1.31(0.44- 2.45)	10.23(5.98- 14.02)	4
	190-4B-111	62	12.90(11.10-14.70)	9.62(3.33-16.40)	30.43(22.30-35.40)	64.30(56.50-68.00)	112.79(93.23-122.43)	5
G.C.	NPH	53	4.69(2.90- 6.05)	13.07(5.69-19.75)	7.36(6.20- 8.56)	5.04(3.17- 7.77)	30.19(18.67- 39.94)	4
	2958	60	1.93(0.27- 6.50)	8.71(7.84-10.45)	8.61(4.86-12.30)	6.87(1.55-16 58)	26.12(24.59- 30.62)	4
	190-4B-111	46	3.56(2.59- 4.47)	1.24(0.63- 1.70)	0.64(0.13- 1.79)	5.99(0.98-11.40)	12.92(5.16- 20.61)	4

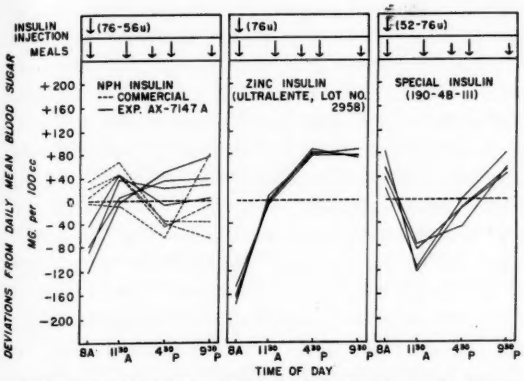

FIGURE 2. Patient H.S.—Patterns of distribution of insulin activity for four consecutive days of single daily doses of three different types of modified insulin, as measured by the patterns of intra-daily variation in blood sugar response.

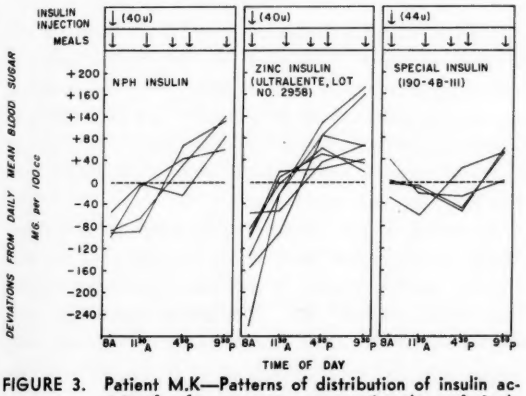

FIGURE 3. Patient M.K—Patterns of distribution of insulin activity for four to seven consecutive days of single daily doses of three different types of modified insulin, as measured by the patterns of intra-daily variation in blood sugar response.

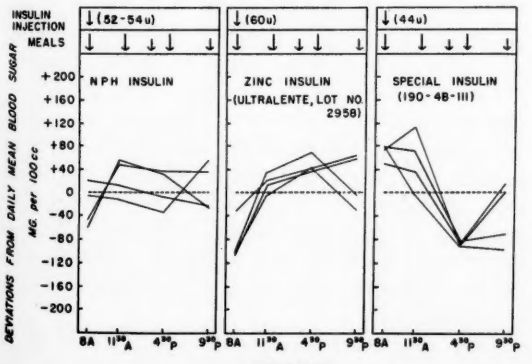

FIGURE 4. Patient G.C.—Patterns of distribution of insulin activity for four consecutive days of single daily doses of three different types of modified insulin, as measured by the patterns of intra-daily variation in blood sugar response.

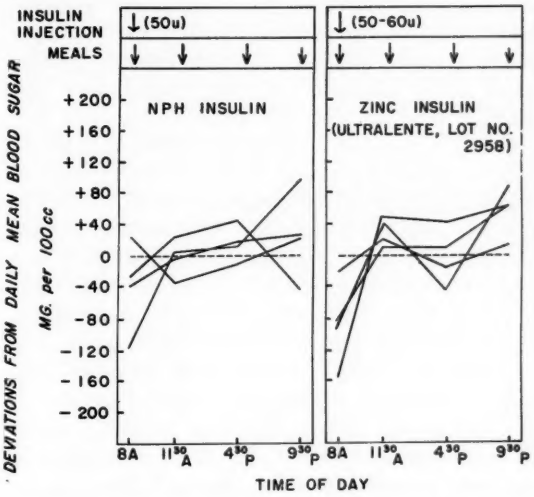

FIGURE 5. Patient H.W.—Patterns of distribution of insulin activity for four consecutive days of single daily doses of two different types of modified insulin, as measured by the patterns of intra-daily variation in blood sugar response.

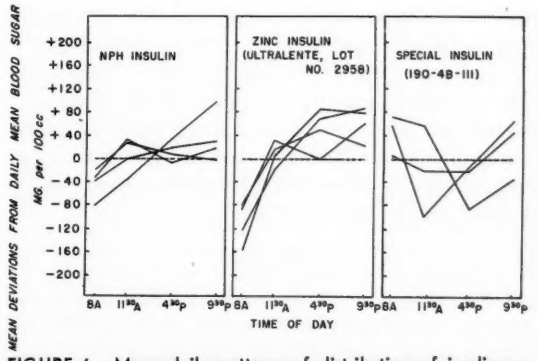

FIGURE 6. Mean daily patterns of distribution of insulin activity of single daily doses of three different types of modified insulin as measured by the mean patterns of intra-daily variation in blood sugar response in each of the four patients with unstable diabetes (H.S., M.K., G.C., and H.W.). Each line represents the average of days in which each patient received the given insulin.

at least four consecutive days for each insulin in Patients H.S., M.K., G.C., and H.W. respectively. The average or mean daily pattern for each insulin in each patient is shown in Figure 6. Each line in Figure 6 represents the average over-all days in which the patient received the given insulin.

A visual inspection of the data indicates that the pattern of intra-daily variability of the blood sugar is affected differently by the insulins studied. The pattern

of Insulin 190-4B-111 displays a consistent tendency toward low points at 11:30 a.m. or 4:30 p.m. and high points at 8:00 a.m. or 9:30 p.m., whereas Insulin 2958 has a consistent tendency toward very low points at 8:00 a.m. and high points at 4:30 p.m. and 9:30 p.m. In contrast, although the pattern of NPH insulin is qualitatively similar to that of Insulin 2958, it is more nearly level. The consistency of the patterns is seen not only in the successive daily patterns in each patient (Figures 2-5), but also in the mean daily patterns from patient to patient (Figure 6). Differences in timing of two different lots of NPH are illustrated in Figure 2 (Patient H.S.). NPH commercial produced a slightly concave type of pattern while NPH Exp. AX-7147-A produced a slightly convex type of pattern.

3. As expected, no large differences in clinical timing of Insulins NPH, 2958 and 190-4B-111 were noted in the seven patients with stable diabetes followed in the clinic. The results in the thirteen patients with unstable diabetes were in accord with the observed patterns of distribution of activity for each insulin. Post-prandial glycosuria was definitely less well-controlled with Insulin 2958 than with NPH. Attempts to correct the post-prandial glycosuria by increasing the dose of Insulin 2958 were apt to produce nocturnal hypoglycemia. On the other hand, Insulin 190-4B-111 had a strong tendency to produce hypoglycemia in the middle of the day. At the same time the action was too weak or absent overnight to control the pre- and post-breakfast sugar levels adequately. These tendencies were more striking in some patients than in others.

COMMENTS

The solubility curves are in good agreement with and serve to complement the respective daily patterns of distribution of insulin activity and clinical behavior of the insulins studied. The results with all three methods of comparison clearly show that Insulins NPH, 2958 and 190-4B-111 display appreciable pharmacologic and clinically significant differences in timing. Insulin 190-4B-111 was found to be considerably faster, while Insulin 2958 was found to be definitely slower than NPH insulin in timing.

The concave type of pattern in distribution of activity of Insulin 190-4B-111, that is, low blood sugar levels in the middle of the day and high levels at night and during the morning, is consistent with its physical characteristics of being already in solution and probably only partially precipitated at the depot site. The "overlapping" effect from dose to dose, which is considered important in a long-acting type of preparation to control post-breakfast hyperglycemia and glycosuria, is lacking. In short, Insulin 190-4B-111 appears to suffer in an exaggerated form from what in our experience has been a consistent defect of clear preparations in general, namely: insufficient prolongation of action to span 24 hours adequately in the majority of patients with unstable diabetes. The pattern of Insulin 2958 is in certain respects opposite to that of Insulin 190-4B-111, that is, high levels during the day and low levels overnight and in the morning. The markedly convex type of pattern produced by Insulin 2958 as contrasted with the more nearly level pattern of NPH insulin is consistent with the much slower rate of solubility in serum of Insulin 2958 than NPH insulin.

The proximity and similarity in contour of the solubility curves of Insulin 2958 and standard PZI are paralleled by the similarity in daily patterns of distribution of activity of Insulin 2958 and those of standard PZI[7]. While the solubility of Insulin 2958 is too slow for the majority of unstable diabetics the significant feature is that a preparation at least as long-acting as standard PZI can be obtained by pure insulin and zinc alone in proper concentration and buffering media. In this respect the present studies fully confirm the reports of Hallas-Moller and associates.

According to the Danish group, three types of zinc-insulin preparations with different ranges of clinical activity can be prepared. These have been designated as "Semilente," "Lente" and "Ultralente." Semilente is a suspension of crystalline insulin in the amorphous state with a reported action range of 12 to 14 hours. Ultralente (somewhat similar to Insulin 2958) is a suspension of crystalline insulin crystals with an action range beyond 30 hours. Lente is a suspension of crystalline insulin, partly in the amorphous and partly in the crystalline state and is said to have the widest range of application with an action range of about 24 hours. Preliminary studies on the solubility curves of suspensions of crystalline insulin in the amorphous state, crystalline state and mixtures of the two indicate that it is possible to obtain a spectrum of solubility speeds in serum with Semilente at one extreme and Ultralente at the other. These studies, together with the respective patterns of daily distribution of insulin activity of different zinc-insulin types, are now in progress and will be reported later.

From a practical standpoint, suitably timed zinc-insulin preparations might have certain advantages over NPH type insulin, such as: (a) possibly more consistent and uniform absorption from the subcutaneous depot; (b) fewer hypersensitivity reactions because of absence

of protein (protamine) modifying agent and purity of insulin; (c) greater flexibility in adjusting optimal timing. Although a single daily dose of NPH insulin tends to produce a nearly level pattern in distribution of insulin activity in the majority of patients in the unstable group, in some cases it produces a convex type of pattern with high sugar levels during the day and low levels during the night and morning, whereas in a few cases it produces a concave type of pattern with low levels during the middle of the day and high levels during the night and morning. The convex pattern may usually be flattened by supplementing NPH insulin with unmodified insulin either in the same syringe or as a separate injection. To flatten the concave pattern it is necessary to split the NPH dose, a larger dose being given before breakfast and a smaller one before supper. The latitude in timing afforded by different types of zinc-insulin suspensions suggests that it may be theoretically possible to treat these smaller but important subgroups with a single daily injection of a suitably timed zinc-insulin preparation.

In spite of the potentialities of the zinc-insulin type of preparations it should be remembered that they suffer from the same limitations of any type of preparation with fixed timing. While type of insulin may influence the daily pattern of distribution of insulin activity as measured by the pattern of intra-daily variability, it cannot control the extent of the variability of blood and urinary sugar responses or, in other words, stability.

SUMMARY

The timing properties of two new long-acting types of experimental insulin preparations: (1) Insulin 2958, a neutral suspension of crystals of insulin and zinc, somewhat similar to the Novo preparation designated "Ultralente," and (2) Special Insulin (190-4B-111), a clear acid solution of chemically modified insulin, were compared with those of NPH insulin. The studies include a comparison of: (1) solubility properties in serum, (2) daily patterns of distribution of insulin activity in patients with unstable diabetes, and (3) behavior in patients in the clinic under routine conditions.

The results with all three methods of comparison are in good agreement and clearly indicate that Insulin 190-4B-111 is considerably faster in timing than NPH insulin whereas Insulin 2958 is definitely slower. Insulin 190-4B-111 was found to have a strong tendency to produce a concave type of pattern of distribution of insulin activity, that is, low levels of blood sugar in the middle of the day and high levels at night and in the morning. On the other hand, Insulin 2958 had a consistent tendency to produce a decidedly convex type of pattern, namely, high levels during the day and low levels at night and in the morning. In agreement with previous studies, NPH Insulin produced a more nearly level daily pattern of distribution of insulin activity.

The present studies confirm in part the reports of Hallas-Moller et al that long-acting preparations with different ranges of activity can be obtained by suspensions of pure insulin and zinc under proper conditions. Studies on suspensions of insulin and zinc with different ranges of activity suitable for clinical use are in progress and will be reported later. The practical implications of suitably-timed zinc insulin suspensions are discussed.

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DISCUSSION

FRANKLIN B. PECK, M.D. (*Indianapolis*): Dr. Izzo should be congratulated on the design of a clinical experiment which will so definitely separate various time actions of insulins.

The number of possible modifications of insulin is almost unlimited. Most of those previously tested have been combinations of insulin with precipitating agents. The latter have included oils, organic compounds such as hexamine, chloroform and various dyes, and combinations devised to slow absorption. Since 1935 the protein precipitants, the protamines, histones and globins have been studied most intensively and have been widely utilized in extending the action of insulin. These compounds cover a wide range of activity and systematic large scale studies have demonstrated that the ones acting in the range of about 2 parts of insulin to 1 part of protamine zinc insulin (mixed) are most practical for general use. It was on this basis that NPH insulin was developed.

One might therefore question what advantage another modification could have. From Dr. Izzo's report it is apparent that neither of the two new modifications fall into the group displaying the best timing characteristics, in that the insulin-zinc suspension acts more like protamine zinc insulin, whereas the chemical modification is too short in action in comparison with NPH insulin. In our own preliminary studies with insulin-zinc suspension one preparation was so slow that it exerted its maximum effect on the fourth morning following a single dose.

Interest in such a preparation as this is two-fold. In the first place, insulin-zinc suspension is composed of crystals formed under special buffering conditions, and has no added protein, owing its long effect to the insulin and component zinc, a normal physiological metal. The range of timing can be shortened, and we are at present working with a preparation having a timing almost like that of NPH insulin. Secondly, there is the possibility that such a preparation may bring at least part of the unstable cases having concave and convex blood sugar curves into the flat curve or stable group. This was suggested by Hallas-Moller on the basis of clinical experience in Denmark. Whether or not this proves to be the case will have to be determined by further studies.

The Use of Potassium in Diabetic Acidosis

There is wide difference of opinion and practice concerning methods of administration of potassium to patients who are recovering from diabetic acidosis. This is understandable. There is no way of estimating with any precision the magnitude of the deficits that are to be corrected nor the rate at which the previously sustained losses can be replaced safely.

Certainly, in some cases, the cells are avid for potassium, so that amounts may be retained that are far in excess of what would be necessary merely to elevate the concentration of potassium in extracellular fluid from a low level to a normal level. This is illustrated by the work of Danowski and associates, who found retention of large amounts of administered potassium in a study of seven patients during recovery from diabetic acidosis. The amounts retained varied from 108 to 450mEq. in periods of 22 to 37 hours; however, since the deficit of potassium may vary widely in different cases, and since the hazards of hyperpotassemia are impressive, we at present administer potassium at a conservative rate of approximately 20 to 25mEq. per hour.

The total amount administered up to the time when sufficient clinical improvement permits stopping intravenous administration of fluid often does not exceed 100 mEq. If necessary, the level of the serum potassium can be determined by flame photometry at any time during treatment, or it can be estimated from the electrocardiogram. As already indicated, the former method is preferable.

Since deficiency of potassium is associated with deficiency of phosphorus, both substances can be supplied in the form of a buffered solution of potassium phosphate. At present we are employing an aqueous solution containing 2.0 gm. of dibasic potassium phosphate and 0.4 gm. of monobasic potassium phosphate in each 5 cc. ampul. This provides 25.89 mEq. of potassium and a mixture of monohydrogen and dihydrogen phosphate (14.4 mM. of phosphate).

The contents of one ampul are added to whatever fluid is being adminstered intravenously at the time, and the rate of flow is adjusted to permit injection of potassium and phosphate at the desired rate. This preparation is preferable to potassium chloride, since the latter may provide an unwanted amount of chloride along with the wanted amount of potassium.

From *Electrolyte Metabolism in Diabetic Acidosis,* by Randall G. Sprague, M.D., and Marschelle H. Power, Ph.D., in The Journal of the American Medical Association, March 21, 1953.

Comparison of Globin Insulin and NPH Insulin

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In articles formerly published, the need for standardized and well-established control of diabetes mellitus in the child has been emphasized, not only for the management of the disease, but also as a prerequisite for evaluating variations in treatment[1-6], including efficacy of the newer forms of insulin.

Children with diabetes mellitus of recent onset have a relatively uniform response to treatment. Approximately five weeks of hospitalization with trained personnel is required to stabilize a child with diabetes mellitus. During this period of management the child's nutritional status is restored and the insulin requirement becomes known.

Figure 1 demonstrates graphically the various phases of stabilization during this period of hospitalization. The period of time necessary to achieve aglycosuria and normoglycemia is called the stage of rapid clinical improvement (Stage I). The period of time during which the insulin requirement decreases gradually is called the stage of metabolic recovery (Stage IIA). Frequently, the insulin dose is decreased below the insulin requirement and minimal glycosuria recurs. This stage is called the transitional period (Stage IIB). The insulin dose is then raised to that level necessary to maintain aglycosuria and normoglycemia. The patient thus passes through a transitional period to the stage of excellent control of the disease (Stage III).

Subjects used for this study were limited to diabetic children in Stage III.

HISTORY

Until 1944 this clinic used regular insulin to maintain stability of control[3]. Injections were given four times daily one-half hour before meals and once during the night, usually at 1 a.m. Since 1944 it has been found practicable to use globin insulin with zinc one hour before the evening meal, replacing the evening and night doses of regular insulin[3]. These studies show that the major action of small doses of U-40 globin insulin subsides within 14 to 16 hours, with some action as long as 18 to 20 hours.

The NPH insulin, which was first introduced in this country by Peck in 1946, is a buffered suspension of protamine zinc insulin crystals, prepared under isophanous conditions according to methods developed by Krayenbuehl and Rosenberg in Hagedorn's laboratory. The crystals are quite stable under proper conditions but change rapidly in the presence of serum[7, 8].

Controversial evidence of clinical differences in timing between globin insulin and NPH insulin has been presented in the literature[9-19]. These differences seemingly are related to the stability and severity of the patient's disease. Reports have indicated that NPH insulin exerts an effect for at least a full 24 hours and probably 28 to 30 hours with the period of maximum action occurring slightly later than for globin insulin[12, 13]. However, it has been emphasized that differences in timing of the various longer-acting insulins tend to be minimized in stable patients and accentuated in the unstable patient[14]. A study of the response of stabilized diabetic children, under well-controlled conditions, to globin and NPH insulin is presented in this paper.

METHOD OF HOSPITAL STUDY

Subjects used for this study were limited to diabetic children living under controlled conditions in the hospital. A specially trained staff was employed in order to attain accuracy in dosage of insulin, site and depth of injection as well as standardization of exercise, collection of specimens of urine and recording of any variable factors which might arise during the period of study. Competent dieticians were responsible for calculating diets and weighing and preparing food. All urine voided was analyzed by laboratory technicians, who also determined the blood sugar levels of the patients throughout the 24 hours on two days each week. Samples of blood for estimating blood sugar

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This study was supported, in part, by research grants from Burroughs Wellcome and Company, Inc., and Eli Lilly and Company.

Address communications to Doctor Jackson at the above address.

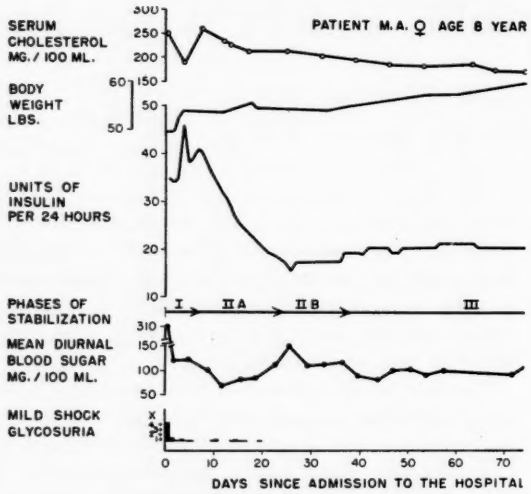

FIGURE 1 **Typical response to treatment of a child with diabetes mellitus of recent onset. Mean diurnal blood sugars represent the average of seven serial blood sugar determinations during a 24-hour-period. Degree of glycosuria represents the average qualitative values of the four daily fractional urine specimens. The phases of stabilization are defined in the introduction.**

values were obtained at the following hours: 7 a.m., 9 a.m., 11 a.m., 4 p.m., 10 p.m., 2 a.m., and 6 a.m. All subjects used were emotionally stable, and the amount of exercise was controlled. No infections occurred during the period of study. Each child was observed for a period sufficient for the insulin requirements to become constant for the standard condition imposed by the therapeutic regimen. All subjects remained free from both glycosuria and clinically significant insulin reactions and maintained approximately normal diurnal blood sugar fluctuations during the period of study.

Five children served as subjects for the first part of this study. Each child was observed for at least two weeks in Stage III. During one week the subjects were given globin insulin one hour before the evening meal, and the other week they received NPH insulin in place of the globin insulin (approximately 43 per cent of the total dosage). Regular insulin was administered one-half hour before the morning and noon meals approximately (35 and 22 per cent respectively). The distribution of the diet was identical and consisted of equicaloric meals, with half of the milk (146 calories) taken from the evening meal and given three hours later.

The diurnal blood sugar values observed during each period are given in Table 1, and the mean values for each of the observations periods and the standard error of difference of the paired control and experimental values are given in Table 2.

TABLE 2

Mean and standard error of difference of paired values of the diurnal blood sugars of five hospitalized diabetic patients in excellent control during a control and an experimental period

Time of observation	Number of observations	Control* period mean	Experimental* period mean	Standard error of difference of paired values
7 A.M.	5	92	104	8.2
9 A.M.	4	94	110	24.0
11 A.M.	5	78	73	5.5
4 P.M.	5	103	126	9.1
10 P.M.	5	106	128	18.0
2 A.M.	5	87	90	11.0
6 A.M.	4	116	98	17.0

*During the control period two doses of regular and one of globin insulin were administered, and during the experimental period two doses of regular and one of NPH insulin were administered.

TABLE 1

Diurnal blood sugar values of five hospitalized diabetic patients in excellent control during a control and an experimental period

				Blood sugar mg. per 100 ml.													
				Control period*							Experimental period*						
				A.M.			P.M.		A.M.		A.M.			P.M.		A.M.	
Subject	Age at onset yrs-mos	Duration of disease at admission	Insulin dosage Units per 24 hours	7	9	11	4	10	2	6	7	9	11	4	10	2	6
M.A.	8-7	2 wks	22.6	110	101	56	109	115	78	129	100	56	59	122	168	107	98
A.F.	4-7	7 wks	12.8	84	—	115	96	144	72	81	95	120	91	96	110	75	110
S.K.	10-7	2 mos	26.0	111	106	59	56	64	98	—	114	146	72	110	126	74	91
D.S.	10-11	4 mos	20.8	64	66	67	127	54	66	99	94	60	52	135	78	91	86
R.U.	4-9	1 mo	10.4	89	104	94	128	154	120	156	116	166	91	169	156	104	104

*During the control period two doses of regular and one of globin insulin were administered, and during the experimental period two doses of regular and one of NPH insulin were administered.

A statistical analysis of the level of blood sugar maintained during the experimental and control periods showed no significant difference between the time action of globin and NPH insulin.

Figure 2 shows the mean values of the diurnal blood sugars for the control and experimental periods compared with the range of 12 diurnal blood sugar determinations observed in six nondiabetic children, and also in relation to the area represented by the mean plus and minus one standard deviation of 176 diurnal blood sugar values observed in 55 hospitalized diabetic children in excellent control. These data in the latter group were compiled by the authors from blood sugar values observed in diabetic patients receiving four doses of regular insulin, two doses of regular and one of globin insulin, or two doses of regular and one of NPH insulin.

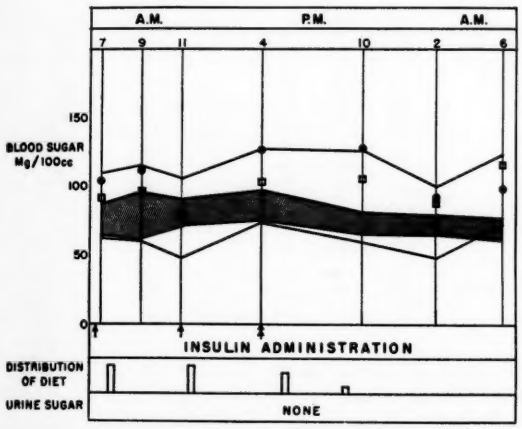

FIGURE 2 The cross-hatched area represents the range of 12 diurnal blood sugar values observed in 6 nondiabetic children. The area between the two black lines represents the mean plus and minus one standard deviation of 176 diurnal blood sugar values observed in 55 hospitalized diabetic children in excellent control. The open squares and solid dots represent the mean of the diurnal blood sugar values of 5 hospitalized diabetic children in excellent control for a control and an experimental period respectively. During the control period two doses of regular and one of globin insulin were administered, and during the experimental period two doses of regular and one of NPH insulin were administered.

Ten additional hospitalized diabetic patients in the past year have received NPH instead of globin insulin in the same regimen of therapy as previously described. In order to expedite their discharge from the hospital, a control series with the use of globin insulin was omitted. The diurnal blood sugar values, with means and standard deviations of the ten hospitalized patients in excellent control receiving two doses of regular and one of NPH insulin, are shown in Table 3. As a basis for comparison, the mean diurnal blood sugar values of ten hospitalized diabetic children in excellent control receiving two doses of regular and one of globin insulin are shown in Table 4, as reported by Jackson and McIntosh in 1945[3]. Figure 3 shows the mean values for each of these groups of patients and a zone representing the mean plus and minus one standard deviation of the group receiving two doses of regular and one dose of globin insulin. The regimen used in 1945 was identical with our present regimen of therapy. The same percentage distribution was used as in the previous study, so that the values obtained could be compared. As can be seen from the chart, the 11 a.m. blood sugar values tend to be somewhat low and the 4 p.m. blood sugar values somewhat high. This could be altered easily by decreasing the morning dose and increasing the noon dose of regular insulin to approximately 33 and 24 per cent respectively. Local reaction did not occur with either NPH or globin insulin.

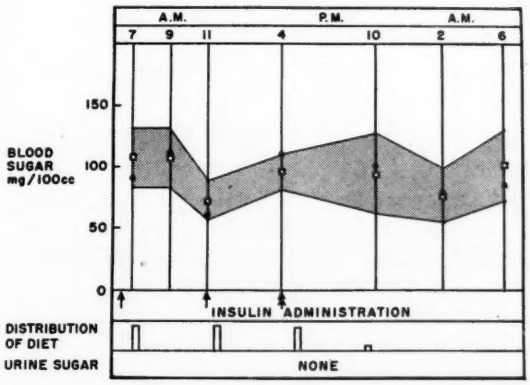

FIGURE 3 The open squares and shaded area represent the mean and plus and minus one standard deviation respectively of the diurnal blood sugar values of ten hospitalized diabetic patients in excellent control receiving two doses of regular and one of globin insulin. The solid dots represent the mean of the diurnal blood sugar values of ten hospitalized diabetic patients in excellent control receiving two doses of regular and one of NPH insulin.

COMMENTS

The data show that NPH insulin can be used interchangeably with globin insulin in well-stabilized diabetic subjects without altering significantly the diurnal blood sugar values. In this study, approximately 43

TABLE 3

Diurnal blood sugar values of ten hospitalized diabetic patients in excellent control receiving two doses of regular and one of NPH insulin

Subject	Age at onset yrs-mos	Duration of disease at admission	Insulin dosage Units per 24 hours	Blood sugar mg. per 100 ml. A.M. 7	A.M. 9	A.M. 11	P.M. 4	P.M. 10	A.M. 2	A.M. 6
M.A.	8-7	2 wks	18.8	109	94	99	91	156	108	120
			17.6	115	122	94	112	86	114	120
			17.6	95	117	133	156	88	120	99
			23.6	100	56	59	122	168	107	98
			22.0	82	104	62	151	90	67	101
R.C.	14-1	3 mos	25.0	81	—	62	109	115	91	122
M.B.	3-9	2 wks	19.2	62	115	48	87	25	42	48
S.Ku.	4-8	1 mo	24.0	125	107	—	72	42	28	36
			23.8	81	161	39	91	94	39	83
			22.6	92	120	44	—	36	—	18
			22.6	36	109	57	—	55	39	65
D.S.	10-11	4 mos	16.4	94	60	52	135	78	91	86
A.F.	4-7	7 wks	10.4	95	120	91	96	110	75	110
			12.0	109	151	33	172	125	141	103
R.F.	7-0	1 wk	28.0	82	—	38	144	117	96	98
R.U.	4-9	1 mo	10.0	116	166	91	169	156	104	104
			10.0	75	29	52	120	73	68	62
			14.8	116	83	52	127	170	99	102
K.L.	9-11	1 mo	35.0	78	91	47	114	99	42	52
			33.0	91	65	47	112	83	65	55
			24.0	93	68	34	112	78	88	117
			22.6	74	—	57	172	94	65	83
			21.6	83	94	59	135	159	70	101
			22.4	96	150	57	88	99	135	125
			21.4	60	117	60	—	39	42	36
S.Ki.	10-7	2 mos	26.0	111	137	31	126	90	67	78
			26.0	98	154	129	84	171	42	81
			26.0	118	148	56	120	118	112	115
		Number of observations		28	25	27	25	28	27	28
		Mean		92	110	62	121	101	80	86
		Standard deviation		20.0	36.0	27.0	28.5	42.0	32.0	29.5

TABLE 4

Mean diurnal blood sugar values of ten hospitalized diabetic patients in excellent control receiving two doses of regular and one of globin insulin[3]

	Blood sugar mg. per 100 ml. A.M. 7	A.M. 9	A.M. 11	P.M. 4	P.M. 10	A.M. 2	A.M. 6
Number of observations	8	11	10	9	11	11	9
Mean	108	108	72	96	94	77	102
Standard deviation	23.9	24.0	16.6	14.3	33.2	21.6	27.9

per cent of the total daily requirement of insulin was administered as globin or NPH insulin. In the first group of patients each patient was used as his own control, and the average amount of globin or NPH insulin given in 24 hours was less than 10 units. In the second group of patients receiving NPH insulin, the diurnal blood sugar values were compared to a similar group of patients receiving globin insulin. The average amount of NPH and globin insulin used in the second group was 9.2 units and 16.6 units respectively. These are relatively small amounts of insulin, and it may be that with larger doses of insulin minor differences would be observed[15]. However, we have found that the insulin requirement of a stabilized diabetic child is intimately interrelated with body weight provided the child is in good nutritional status[20]. Patients in this study were observed under controlled conditions, and any major differences of time action should have become apparent.

SUMMARY

No significant differences in the diurnal blood sugar curves were observed for groups of well-regulated diabetic children receiving globin zinc insulin or NPH insulin administered one hour before the evening meal in the same percentage distribution.

We wish to express indebtedness to Helen G. Kelly, M.S., for statistical consultation and helpful suggestions in the preparation of this paper.

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Disaster Feeding

Natural disasters are not strangers to this country. Many people have been killed or injured and thousands have become temporarily homeless as a result of fire, flood, windstorm or earthquake. Various organizations, especially the Red Cross, have had extensive experience in feeding and otherwise caring for people under such conditions. Man-made disaster such as an enemy could inflict on this country today represents an experience which the American people have not yet had to endure. Likewise, no American organization has had experience in meeting this type of disaster.

The physical, medical and psychological problems posed by atomic, biological or chemical warfare, or even massed conventional and fire bombing are of a type and magnitude which demand special thought, planning and organization if they are to be met sucessfully. It is such considerations which led to the establishment of a Civil Defense Organization in the United States.

A vital part of every Civil Defense plan must be for disaster feeding. The prompt provision of warm food and drink for the injured and homeless is a must if morale is to be maintained, panic avoided and the stricken community restored to a functional state in a minimum of time. As this communication will attempt to show, disaster feeding is important for reasons other than just to give nourishment to those who cannot provide for themselves. It is an effective means of therapy, a tool for mass therapy, which should rank in importance with the medical treatment of the injured. Indeed, it is an important factor in such treatment.

As is well known, a lack of drinking water will produce death far more quickly than a complete lack of food. For this reason a high priority should be given to the provision of an emergency supply of potable water. It is well established that adults, previously well nourished, can withstand many days of fasting without harm. They can even maintain moderate activity at the expense of some loss in body weight.

From *Disaster Feeding,* by James M. Hundley, M.D., in The Journal of the American Medical Association, April 18, 1953

Studies of Radioactive Insulin

Neil J. Elgee, M.D.†, Robert H. Williams, M.D., Norman D. Lee, Ph.D., Thomas Wong, M.D., and John R. Hogness, M.D., Seattle

Highly purified crystalline insulin was labeled (and hereinafter noted as insulin*) by iodination with radioactive iodine (I^{131}), presumably on the tyrosine rings, by the method of Ferrebee et al.[1] The material was hypoglycemic to rabbits and assayed according to prediction by the rat diaphragm-glucose uptake technic[2]. The radioactivity stayed with the protein fraction in trichloracetic acid precipitation, in dialysis and in chromatography, and had the same mobility as unlabeled insulin in paper electrophoresis. Therefore the label did not alter certain measurable properties of the insulin.

Distribution studies in the rat fifteen minutes after intravenous administration of insulin* showed the greatest concentration to be in the renal cortex. Thyroid (presumably largely free I^{131}), liver and stomach also showed concentrations higher than plasma. Muscle concentration was not striking but total muscle mass was such that 30 to 50 per cent of the material was in that locus. Brain showed a notably low concentration, and red blood cells none at all. There was very little in the urine. It concentrated in the placenta and a small amount entered the fetus. A small but significant fraction was absorbed into the blood when insulin* was injected into the small intestine.

Studies of the subcellular fractions of liver, kidney and muscle showed that insulin* had entered the cell. It was distributed in the cytostructural elements of the liver in a characteristic manner and fixation on the subcellular particles was shown to depend on cellular integrity. Control studies with I^{131}-labeled human serum albumin, and with I^{131} alone, showed totally different patterns of distribution.

Several experiments were designed to explain the high concentration of the radioactivity in the kidneys. Radioautographs showed it to be concentrated primarily in the convoluted tubules. Simultaneous injection of a glucose load with the insulin* resulted in less radioactivity in the kidneys. Interruption of the glucose reabsorptive system with phlorizin effected only a slight reduction in renal insulin.* Adrenalectomy had no effect on the concentration; however, hypophysectomy decreased it markedly—perhaps on the basis of decreased renal blood flow. These data make one consider the possibility that the kidney may play some role in the breakdown or inactivation of insulin.

Since the labeled insulin was non-dialyzable and was precipitable with trichloracetic acid, it was assumed that dialyzable and non-precipitable fractions represented breakdown products of the molecule. Chromatography demonstrated that one of these fractions was iodide, but there were several additional unidentified fractions. Since we have not correlated these degradations with changes in biologic activity of the insulin, we cannot state to what extent the degradation has influenced this activity. The rate of fall of blood "insulin"* (that is, trichloracetic acid precipitable or non-dialyzable radioactivity) was studied in an attempt to measure insulin breakdown. In rats, with surgical nephrectomy, or with physiological hepatectomy, the fall in blood "insulin"* was diminished. Thus it would seem that in the rat, both liver and kidney play a role in insulin breakdown.

Tissue concentrations in the human were studied, the insulin* having been given shortly before demise. In general, the concentrations found were similar to those in the rat, with high concentrations in kidney, liver and stomach. In two patients with cirrhosis, de-

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creased hepatic concentrations were found. The rate of fall of blood "insulin"* after an intravenous infusion with glucose, in normal humans and in various patients was studied. Preliminary results suggest that in kidney and liver disease there may be a decrease in the rate of fall of blood "insulin"*. A decrease in the rate of fall was seen in some old and young diabetics. This was of greater extent in a patient with insulin resistance, and in a diabetic whose insulin requirement dropped to zero in the presence of cirrhosis.

A recent bioassay of the labeled insulin, kindly performed by Eli Lilly & Company, has shown that there is some reduction in its biological activity. This finding, and its relation to the results above, are being further investigated.

SUMMARY

Studies have been conducted on certain aspects of the metabolism of I^{131}-labeled insulin in rats and man. The work thus far has served largely to indicate new avenues for investigation: the role of intracellular insulin, of renal insulin, of insulin inactivation and breakdown, and the role these metabolic pathways play in clinical problems.

ACKNOWLEDGEMENTS

We are grateful to the Eli Lilly Company for their assistance, including a supply of the crystalline zinc insulin.

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DISCUSSION

PETER H. FORSHAM, M.D. (*San Francisco*): This excellent study using the most modern technics has markedly expanded the pioneer work done along these lines in Great Britain. We might discuss some of the clear-cut findings obtained by these investigators in the light of our present-day knowledge of intermediary metabolism derived from isolated systems such as tissue slices, cell homogenates and extracts. These have their limitations, for as Szert Gyorgyi pointed out, the cell membrane and intact intracellular structure preserve common energy levels which allow for chain reactions and the most economical utilization of intracellular energy. Disruption of morphology brings with it the disappearance of these common energy levels and the destruction of super highways of intermediary metabolism. In using the isotope technic, as was done here, the working mechanisms of the undisturbed cell are penetrated and the gap which arises when cellular integrity is jeopardized has been bridged.

The labelled insulin used was proved biologically active and that makes the findings highly significant. The cell was penetrated by insulin, which became fixed at strategic points, suggesting a true intracellular function. This would give support to those who believe that insulin acts intracellularly on enzymic mechanisms and not exclusively on the diffusion of glucose into the cell. The latter might be influenced by some intracellular activity of insulin. Could the relative unresponsiveness to insulin in early acidosis be connected with improper fixation inside the deranged cell? Might micelle formation, such as was demonstrated by workers at the Massachusetts Institute of Technology, in acid solutions, play a role?

The findings that both liver and kidney destroy insulin may partly explain the increased insulin sensitivity found in advanced Kimmelstiel-Wilson syndrome where hitherto poor liver glycogen deposition was thought to be the most important factor. It is of interest that red cells and brain were shown to contain little or no labelled insulin and it is known that the red cell has a glycolytic system which does not require hexokinase, and brain tissue has never been affected by insulin in vitro. The finding that the rate of fall in the serum levels of labelled insulin decreased in some diabetics suggests a reduced intracellular penetration or a block to surface fixation by insulin antagonists such as was demonstrated in isolated rat diaphragm by Stadie and his associates. One question that one would wonder about is: Does the rate of administration of insulin alter the distribution?

The authors are to be congratulated on this important fundamental work which will continue to confirm old and open up new physiological concepts as it progresses.

Does Glucose Stimulate Adrenocortical Activity?

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Several investigators [1-7] have reported that glucose is a stress agent capable of stimulating adrenal cortical activity. A depression of the lymphocyte count served as the criterion of corticosteroid discharge though Drury[5] and Jordan, Last, Pitesky and Bond[3] described glucose induced eosinopenia in laboratory animals and Hungerland and Raming[6] and Artunkel[7] reported the latter phenomenon in humans.

Recant et al[8], however, failed to produce a significant fall in circulating eosinophils in eight normal subjects after the intravenous injection of glucose. Steeples and Jensen[9] reported that in the white rat glucose inhibited the release of adrenal cortical hormones and Skelton[10] found no adrenal cholesterol or ascorbic acid depletion after glucose though the response to corticotropin was enhanced.

The possible influence of hyperglycemia on adrenal function and the known intimate relationship of the 11-oxygenated adrenal steroids to carbohydrate metabolism has led to investigation of the physiologic status of the adrenal cortex in diabetes mellitus. Lazarus and his co-workers[11] found that 11 of 22 diabetic patients failed to exhibit lymphocytopenia after intravenous glucose though the remaining 11 and all of the 18 normal controls did show a significant lymphocyte depression. Wilson et al[12] suggested a compensatory hypofunctional state of the adrenals and Field and Marble[13] found reduced adrenal cortical reserve in diabetic patients. In a paper by Talbot and his associates[14] urinary corticoid values in four controlled diabetic subjects were in the same range as hypopituitary subjects and lower than in Addisonian patients; Forbes and her co-workers[15] as well as Miller and Mason[16] reported 17-ketosteroid values in diabetic patients somewhat lower than normal.

The question of the adrenocortical stimulating properties of glucose assumes both practical and theoretical importance. Glucose is a routinely adminstered nutrient in hospital practice. The form of the glucose tolerance curve is generally attributed to extra-adrenal factors; if adrenal stimulation follows glucose administration the role of the adrenal cortex must be considered in the interpretation of tolerance tests. In experimental work glucose-saline mixtures are often administered to "control" subjects on the assumption that the glucose content will exert no endocrine influence. If glucose can be shown to act as a stress agent one might ask whether the somewhat diminished adrenal cortical function noted in diabetes (vide supra) can be attributed to the effects of continuous hyperglycemia producing a secondary exhaustion phenomenon of the adrenal cortex.

The work reported in this article comprises an investigation of the effect of glucose infusions on adrenal cortical function in normal and diabetic subjects using the change in circulating eosinophils as the criterion of adrenal response. Eosinophil counts, though sometimes of limited value in the interpretation of adrenal function in individual cases, are of great value in the study of groups of subjects and are probably the most sensitive available measure of adrenal response in humans to any given stimulus since a maximal eosinopena is induced by small quantities of adrenal steroids[17].

METHODS

Eosinophil responses to glucose were measured in 79 subjects and to saline in 26 subjects as follows: A glucose tolerance test was carried out after an overnight fast in 19 normal and 21 diabetic individuals by giving one-third gram of dextrose per kilogram of body weight in a 50 per cent solution intravenously within 3 to 5 minutes and obtaining 0.1 cc. capillary blood specimens 15, 30, 60, 75, 90 and 120 minutes thereafter. Blood sugar determinations were made by the Nelson modification of the Somogyi-Shaffer-Hartman method[18]. All patients had been on an adequate carbohydrate intake during the week prior to testing.

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The "normal" subjects were individuals who had been referred to the Endocrine Clinic and found to be free of any significant organic pathology, or were nurses from the hospital staff who volunteered. The diabetic subjects were patients from the Metabolic Outpatient Clinic. Circulating eosinophil counts were obtained before and at four hourly intervals after a glucose injection in the first 19 cases, at 2 and 4-hour intervals in the next 10 subjects and finally only at 4 hours in the remaining cases, since it was found that the maximum response was not overlooked by the omission of the 1, 2, and 3-hour count. In several subjects additional counts were obtained at 6 hours. The eosinophil counts were performed upon capillary blood as described by Gershberg et al[19] using Randolph's phloxine-propylene-glycol stain[20], and counted in a Levy-Fuchs chamber; the average of four chamber counts was used in the calculation. Tests were carried out in the fasting state, usually from 8 a.m. to 12 noon. Patients receiving corticotropin or epinephrine were permitted to eat breakfast immediately following the injection of these agents.

In an additional 28 normal and nine diabetic subjects two-thirds to one gram of glucose per kilogram of body weight in a 10 per cent solution in physiologic saline was infused intravenously over a 2-hour period. In eight of these subjecs hematocrit determinations were made before and 4 hours after starting the infusion. Eosinophil counts were obtained before beginning the infusion and 2 hours and 4 hours later. In several cases 6-hour counts were made. Seven of the 28 normal subjects received the entire infusion in one hour. Two normal subjects were given one and one-half to two grams of glucose per kilo in 2 hours. With six normal subjects, 50 cc. of physiologic saline solution was injected intravenously at the same speed as the injection of the smallest dose of glucose (that is, 1/3 gm. per kgm.) and to an additional 20 normal individuals, 1,000 cc. of saline was infused intravenously within two hours. Eosinophil counts were made in these two control groups at zero, 2 and 4 hours. The adrenocortical responsiveness of eight subjects who had failed to exhibit a significant eosinopenia after glucose, was tested by the intramuscular injection of 25 mg. of corticotropin and an additional five patients were tested with 0.3 mg. of epinephrine.

All subjects were in a satisfactory nutritional state. Their ages ranged from 18 to 60 years. Solomon and Shock[21] demonstrated that aged males responded with a fall in circulating eosinophils after the injection of corticotropin as well as young men. None of the individuals tested had been subjected to any significant known stress such as surgery, acute infection, burn, fracture or severe emotional trauma within 3 months prior to these studies.

RESULTS

In Table I the data for the 4-hour eosinophil counts are shown and in Figure 1 the individual counts are illustrated; statistical analysis of the hourly counts did not alter the results and they are not charted. Glucose failed to induce a significant depression of the circulating eosinophils in both the normal and diabetic subjects at all dose levels and there was not any difference noted between the response of normal compared to diabetic patients. The mean eosinophil drop was greater when the larger dose of glucose was administered in both the normal and the diabetic individuals but the differences were not statistically significant. When two-thirds to one gram of glucose was infused only four of 21 subjects exhibited a fall of greater than 50 per cent of the pre-injection value and eight showed a fall of greater than 40 per cent. None of the nine diabetic patients given the larger dose of glucose showed an eosinophil depression of greater than 50 per cent; one fell 46 per cent. Neither of the two normal subjects given one and one-half to two grams of glucose per kilo showed a significant eosinopenia. Column 1 of

TABLE 1

The eosinophil response to the intravenous administration of glucose in normal and diabetic subjects.

Group	Glucose in gm. per kgm.	Approx. vol. and speed of injection	Normal Subjects: Number of Cases	Normal Subjects: Mean per cent fall of eosinophils	Normal Subjects: S.D.	Diabetic Subjects: Number of Cases	Diabetic Subjects: Mean per cent fall of eosinophils	Diabetic Subjects: S.D.
A.	0.33	50cc 3-5 min	19	18	20.98	B.21	17	28.36
C.	0.66	1000 cc 2 hrs	21	30.9	23.31	D. 9	25.2	25.16
E.	0.66	1000 cc 1 hr	7	24.4	18.94			
F.	1.5	1000 cc 2 hrs	2	17				
G.	Physiologic saline solution	50 cc 3-5 min	6	13.8	28.53			
H.	Physiologic saline solution	1000 cc 2 hrs	20	18.9	21.61			
I.	ACTH-25 mg. I.M.		8	55.8	(range 36-86)			

Fisher's "t" values—Groups A-B-0.06, C-D-0.37, A-C-1.11, C-G-1.09, A-F-0.27, B-D-0.59

S.D.=Standard deviation

Figure 1 shows the results of corticotropin tests in the subjects most unresponsive to glucose and demonstrates their normal responsiveness to corticotrophic stimulation; the mean eosinophil fall was 56 per cent. The response to epinephrine was less intense but, since this work was begun, serious doubts have been cast on the validity of the epinephrine test as a measure of pituitary-adrenocortical responsiveness[22].

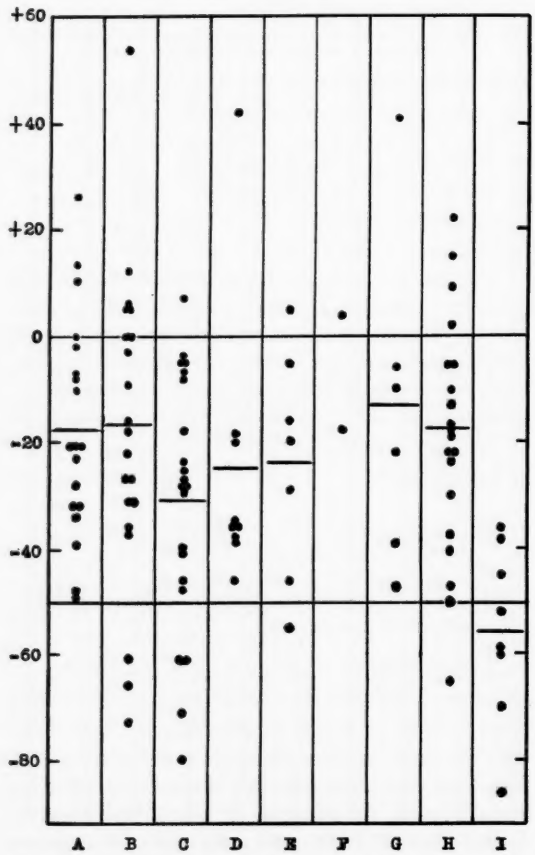

FIGURE 1 Changes in circulating eosinophils in normal and diabetic subjects after intravenous glucose compared to control subjects infused with physiologic saline solution. Letters "A" to "I" refer to the corresponding groups in Table 1. Horizontal bars represent the mean for each group.

No significant correlation could be demonstrated between the maximum rise in blood sugar and the fall in eosinophils (R = 0.17) or between the lowest blood sugar, that is, the maximum hypoglycemic drop after the glucose infusion, and the fall of eosinophils (R = 0.19).

When the larger dose of glucose was administered to nondiabetic subjects the average maximum blood sugar attained was 360 mg. (range 186 to 610 mg.) and the average hypoglycemic drop was 28 mg. below the fasting level (range 12 to 70 mg.). In diabetic subjects the mean maximum blood sugar was 574 mg. (range 420 to 681 mg.). It thus appears that the degree of hyperglycemia attained should have been sufficient to activate the pituitary-adrenocortical system if this were possible with glucose. There was no change in the hematocrit values in the eight patients in whom this was measured.

DISCUSSION

The data obtained fail to reveal any significant eosinopenic effect of glucose infusions in normal or in diabetic individuals. The interpretation of these results must be made with full knowledge of the unreliability of the alteration in circulating eosinophils as a criterion of adrenal cortical function in isolated instances, but, in a series comprising 105 cases, the failure to reveal any statistically significant evidence of the pituitary-adrenocortical activating properties of glucose seems valid. The report of Hungerland and Raming[6], who found a glucose-induced eosinopenia in a small group of cases, was unsupported by a statistical evaluation.

The recent paper of Artunkel and Kayahan[7] stated that the oral administration of 50 gm. of glucose to 10 normal subjects and to 10 diabetic patients resulted in a two-phased eosinopenic response. The initial fall was noted 30 minutes after glucose administration and was less than 50 per cent of the fasting count, and the second fall was at 2 hours. There were no controls. It does not seem valid to ascribe a rapid and transient depression in circulating eosinophils to adrenocortical activation, particularly in view of the labile and variable levels of circulating eosinphils when observed in control patients. An eosinopenia indicative of cortical steroid release is generally maximum only after 2 to 4 hours and is sustained at least 8 hours[23].

The results of this study lead to the conclusion that glucose is not a stress agent and does not induce an adrenocortical response to its short term administration. No conclusions can be drawn from this work as to the possible effects of the prolonged administration of glucose upon the adrenal cortex.

SUMMARY

The effect of glucose infusions on the circulating eosinophil count was measured at 3-dose levels in 49

normal subjects and 30 diabetic patients and compared to 26 normal control individuals infused with physiologic saline solution. No significant eosinopenic response was evoked in either normal or diabetic subjects and it was concluded that, using the circulating eosinophil as an index of adrenocortical activation, glucose was not a stress agent capable of provoking a discharge of corticosteroids in acute experiments in man.

ACKNOWLEDGEMENTS

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Renal Vascular Disease in Diabetes Mellitus

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It is common knowledge that the diabetic state accelerates the development of atherosclerosis in the arteries of the lower extremities, the heart and the kidneys[1]. This study is restricted to the kidneys and is based upon 1,465 autopsies on diabetic subjects.

The renal arteries: The average intensity of atherosclerosis in the renal arteries of diabetic subjects is much greater than in nondiabetics of corresponding age, and in some of the older diabetics narrowing of these vessels is a contributory factor in the production of atrophy of the renal cortex. But in the great majority of kidneys, cortical atrophy is due almost entirely to arteriolosclerosis and intercapillary glomerulosclerosis.

The renal arterioles: An afferent arteriole is defined as the terminal vessel supplying a glomerulus. The vessels from which the afferent arterioles arise are called small arteries. In this discussion arteriolosclerosis refers to the presence of a hyaline subintimal deposit in the afferent arterioles. The arteriolar hyaline varies from a thin subintimal layer with an intact muscular wall (grade 1) to a massive deposit with replacement of the muscle (grade 3) illustrated in Figure 1.

The incidence of arteriolosclerosis in diabetes is shown in Table 1. It appears to be rare before the age of 20 years; the number of reported cases is too small to have much significance. It was found in about one-half of the subjects between 20 and 50 years of age, and in about two-thirds of those over 50 years of age. It is somewhat more frequent in females, and is especially high in females over 50 years of age. There is always an associated intimal atherosclerosis of the small arteries but the severity of the arterial lesion does not correspond with the intensity of the arteriolosclerosis. When the afferent arteriole is severely affected there is frequently a similar but less pronounced hyalinization of the efferent arteriole (Figure 2). The involvement of the efferent arteriole appears to be specific for diabetes. I have not found hyalinization of the efferent arterioles in primary hypertension.

FIGURE 1 An afferent glomerular arteriole showing Grade 3 arteriolosclerosis. The muscle is almost completely replaced by the hyaline deposit.

TABLE 1

Incidence of Renal Arteriolosclerosis in Diabetics With Respect to Age and Sex

Age at Death	No. of Diabetics		Degree of Arteriolosclerosis 0	1	2 & 3	Incidence per cent
0-20 yrs.	M	16	15	1	0	6.2
	F	17	16	1	0	5.9
20-50 yrs.	M	108	49	15	44	54.6
	F	126	72	18	36	42.8
50-90 yrs.	M	564	211	156	197	62.6
	F	634	172	157	305	72.9
Total	M	688	275	172	241	60.0
Total	F	777	260	176	341	66.5
Grand Total		1465	535	348	582	63.5

The relation of renal arteriolosclerosis to hypertension in diabetes. In Table 2 the incidence of arteriolo-

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FIGURE 2 Glomerulus showing hyalinization of both the afferent and the efferent arteriole.

TABLE 2

Renal Arteriolosclerosis in diabetics with respect to age, sex and blood pressure

	Total no. of diabetics	Blood pressure below 150/90 mm. hg.			Blood pressure 150 to 179/90 mm. hg.			Blood pressure 180/90 mm. hg. and higher			Hypertension
		No.	%	+	No.	%	+	No.	%	+	%
Males 20 to 50 yrs	74	35	37		14	86		25	84		52.7
Females 20 to 50 yrs	83	52	25		10	30		21	95		37.3
Males 50 to 90 yrs	455	178	53		157	71		120	78		60.9
Females 50 to 90 yrs	516	166	62		175	72		175	87		67.8
Total Males	529	213	50.2		171	71.9		145	78.6		59.7
Total Females	599	218	53.2		185	69.7		196	88.2		63.6
Grand Total	1128	481	51.7		356	70.8		341	84.2		61.8

sclerosis is shown with respect to age, sex and blood pressure. This group is smaller than Table 1 since the blood pressure was not always recorded. Also a number of cases with low blood pressure were not tabulated since the low reading was obviously due to shock from coronary thrombosis or diabetic coma. It is clear that arteriolosclerosis is much more frequent in association with hypertension, especially in diabetics under 50 years of age; but the number that have arteriolosclerosis without hypertension is impressively high. Over one-half of the elderly diabetics without hypertension have arteriolosclerosis. The circumstance that such individuals without hypertension did not have cardiac hypertrophy indicated that the recorded blood pressure was correct. It is obvious from Table 2 that arteriolosclerosis develops in a large percentage of diabetics in the absence of hypertension, and in this group at least it must be attributed to the diabetic state and not to hypertension.

There is an increased incidence of arteriolosclerosis in hypertensive diabetics which is very pronounced in the group below 50 years of age but less prominent in the older groups (Table 2). This indicates a causal relation between hypertension and arteriolosclerosis. In juvenile diabetics it is a common observation that the blood pressure usually does not increase until after many years of diabetes when the signs of renal disease begin to appear. This is a strong argument that in juvenile diabetes the hypertension is of renal origin as it is in glomerulonephritis.

In the group over 50 years of age, 22 per cent of the males and 13 per cent of the females with very high blood pressure did not have arteriolosclerosis. These may be individuals who had primary hypertension before the onset of diabetes. In the individual case histories it frequently appears that the blood pressure was elevated for several years before the appearance of glycosuria. If we assume that diabetes develops as readily in hypertensive as in nonhypertensive subjects we must believe that hypertension in elderly diabetics is frequently of the primary type.

FREQUENCY OF HYPERTENSION IN DIABETES

John[2] found hypertension (systolic pressure, 150 mm. Hg. or higher) in 26 per cent of 548 diabetic males, and 50 per cent of 533 diabetic females over 40 years of age. Edeiken[3] found hypertension (systolic pressure, 160 mm. Hg. or higher) in 55 per cent of 69 diabetics over 50 years of age, and no hypertension in 31 diabetics below 50 years of age. All of his 100 patients had had diabetes for ten years or longer. Martenson[4] found hypertension (150/90 mm. Hg. or higher) in 48 per cent of 111 men and 65 per cent of 110 women, all of whom had had diabetes at least 15 years. Boas[5] found hypertension (150/90 mm. Hg. or

higher) in about one-third of 289 diabetic males and about 70 per cent of 211 diabetic females over 50 years of age.

My observations indicate that hypertension (150/90 mm. Hg. or higher) was present in 60.9 per cent of 455 diabetic males and 67.8 per cent of 516 diabetic females over 50 years of age (Table 2). The high incidence of hypertension in the younger diabetics of my series is due to the fact that many of them were observed after a long period of diabetes. In the younger diabetics the incidence of hypertension is vastly greater than in nondiabetics of corresponding age, but after the age of 50 years primary hypertension is very frequent in the nondiabetic population. Wetherby[6] found hypertension (150/90 mm. Hg. or higher) in 38 per cent of male and 57.5 per cent of female dispensary patients over 50 years of age. Other observers found a somewhat lower incidence of hypertension in group surveys, but all agree that it is common after middle life and much more frequent in females. The foregoing data indicates that after the age of 50 years diabetes increases the incidence of hypertension in males about 50 per cent and in females about 20 per cent.

The relation of arteriolosclerosis to the duration of diabetes (table 3). The duration of the diabetic state has a striking influence on the development of arteriolosclerosis in juvenile diabetes. In subjects under 40 years of age arteriolosclerosis is infrequent with less than 10 years of diabetes, but it is very common after more than 10 years of the disease. In the groups over 40 years of age the influence of duration is still noteworthy but much less pronounced, especially in those over 60 years of age. In the older groups the lesser effect of duration is in part attributable to errors in determining the time of onset of diabetes. The duration of diabetes in the elderly is usually underestimated since no account is taken of the asymptomatic stage of the disease. A mild diabetes may be unrecognized for years. However, it appears probable that some influence other than the duration of the diabetes is partly responsible for the development of arteriolosclerosis in elderly diabetics.

ETIOLOGY AND SIGNIFICANCE OF ARTERIOLOSCLEROSIS

The conditions which are known to promote the development of renal arteriolosclerosis are age, increased intravascular pressure and diabetes. These influences affect the renal arteries as well as the arterioles.

A. *Age.* In all normal individuals there is a progressive thickening of the intima of the renal arteries with advancing age. This is more pronounced in some than in others, but practically no one over 50 years of age is entirely free of intimal thickening of the renal arteries. Occasionally in advanced life this process extends into the arterioles, and a small percentage of elderly individuals have mild arteriolosclerosis in the absence of hypertension and diabetes.

B. *Increased Intravascular Pressure.* Primary hypertension begins as a spastic condition of the small peripheral arteries and arterioles throughout the body. In the earlier stages of this disease there are no structural changes in the peripheral vessels; but after years of high blood pressure one usually finds a more severe degree of intimal thickening in the renal arteries than is found in nonhypertensive individuals and also some degree of renal arteriolosclerosis. The severity of the arteriolosclerosis varies with the duration and intensity of the hypertension and with unknown factors. Some persons who have had high blood pressure for many years do not develop arteriolosclerosis. In a large group of hypertensive subjects who died of encephalomalacia or intracranial hemorrhage I found arteriolosclerosis in 73 per cent. Arteriolosclerosis cannot be the cause of primary hypertension since it is entirely absent in a large percentage at autopsy, and renal biopsies taken during the early stages of the disease frequently show normal arterioles. It appears well established that increased intravascular pressure (primary hypertension) may cause renal arteriolosclerosis.

C. *Diabetes.* In diabetes, arteriolosclerosis is clearly due to the diabetic state since it was found in over one-half of the nonhypertensive elderly diabetics. In juvenile diabetes the severe involvement of the arterioles and glomeruli causes hypertension; but evidently a simple arteriolosclerosis does not often cause hypertension since a large proportion of elderly diabetics with arteriolosclerosis are nonhypertensive. Primary hypertension in a diabetic would presumably accelerate the development of arteriolosclerosis.

In diabetes the hyaline deposit in the afferent arterioles is usually much thicker than in primary hyper-

TABLE 3

Relation of arteriolosclerosis to the duration of diabetes

Age at death	Total diabetics	Less than 10 yrs			10 to 20 yrs			Over 20 yrs		
		Total	+ No.	+ %	Total	+ No.	+ %	Total	+ No.	+ %
20-40 yrs	108	66	10	15.1	35	27	77.1	7	7	100
40-60 yrs	348	253	138	54.5	72	59	81.9	23	19	82.6
60-90 yrs	787	551	373	67.7	178	147	82.6	58	48	82.8

tension, and when it is as pronounced as in Figure 1 the existence of diabetes is highly probable. We do not know whether arteriolosclerosis without involvement of the glomeruli produces any functional disturbance in the kidney, but there must be some degree of ischemia when the arterioles are severely narrowed. Possibly the proteinuria often found in the absence of glomerular lesions is due to renal ischemia from arteriolar disease. McManus[7] considers arteriolar hyalin a glycoprotein on the basis of its reaction with the periodic acid-Schiff reagent. Frequently some lipid may be demonstrated in the hyalin with a Sudan stain.

INTERCAPILLARY GLOMERULOSCLEROSIS

The term "intercapillary glomerulosclerosis" was introduced by Kimmelstiel and Wilson[8] in 1936, to designate rounded hyaline masses in the intercapillary spaces of the glomerular lobules. The word "intercapillary" seems appropriate since the alteration begins between the capillaries and not within them as in glomerulonephritis. But the term "sclerosis" is not so suitable since to most pathologists it implies an increase of connective tissue. The intercapillary masses cannot be collagen since no collagenous fibers have been demonstrated in glomeruli beyond the vascular pole. A nonprejudiced term such as "intercapillary lesion" might be better, but there is no serious objection to the well-established term, "intercapillary glomerulosclerosis."

The diabetic glomerular lesions are characterized by an accumulation of hyaline material in the intercapillary spaces. When the hyalin is in the form of rounded masses we may speak of the "nodular" type, and when it appears as lineal thickenings it may be called the "diffuse" type.

The nodular type. These lesions, first described by Kimmelstiel and Wilson, are now widely recognized. They consist of rounded hyaline masses in the intercapillary areas of the glomerular lobules. Nuclei are present in the periphery of the mass but the central portion is free of nuclei (Figures 3 and 4). Definite nodules are easily recognized and can hardly be confused with any other lesion. They are almost specific for diabetes, but are found in rare instances in which diabetes cannot be demonstrated. In an occasional case of chronic glomerulonephritis, nodular intercapillary lesions are found which simulate the diabetic lesion in many respects but the nodules are uniformly distributed in the lobules and the afferent arteriole is not hyalinized (Figure 5).

Nodular lesions vary widely in different cases from a small nodule in an occasional glomerulus to almost com-

FIGURE 3 Glomerulus showing both nodular and diffuse intercapillary lesions.

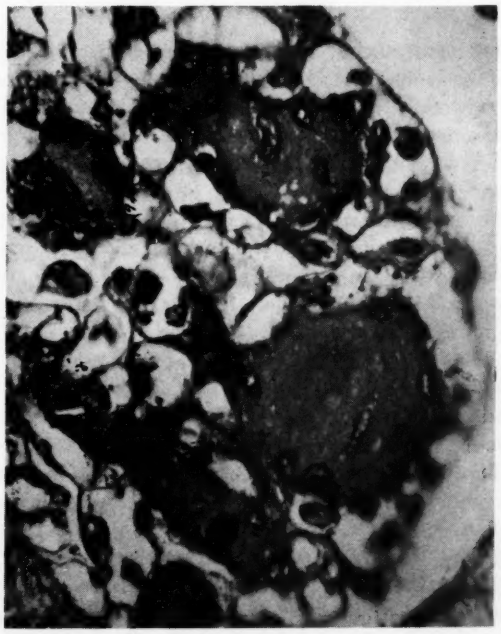

FIGURE 4 An area from Figure 3 under higher magnification. Note the epithelial nuclei in the intercapillary lesions.

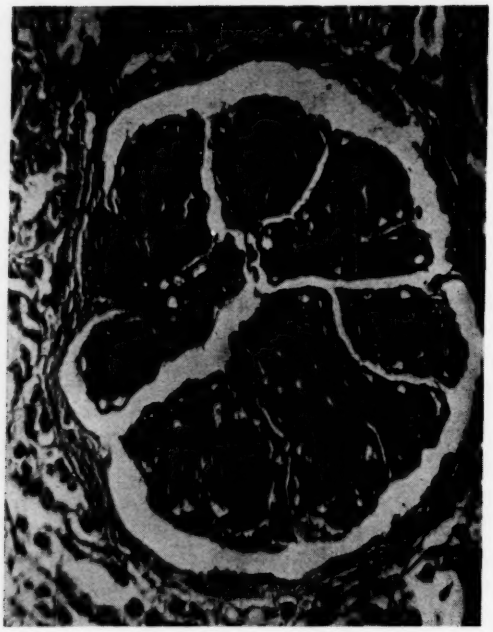

FIGURE 5 Chronic glomerulonephritis showing nodular intercapillary lesions. Note the uniform distribution of the nodules. Compare wth Figure 3.

FIGURE 6 Glomerulus showing mild diffuse intercapillary glomerulosclerosis. Compare with Figure 9.

plete obliteration of a majority of the glomeruli. They are nearly always associated with diffuse lesions and so many transitions are found that a clear distinction between the two types cannot be made. Those who consider only nodular lesions specific for diabetes must make many arbitrary decisions. In many kidneys the intercapillary lesions are largely of the nodular form, but in a majority the nodules are insignificant in comparison with the diffuse lesions. The destruction of glomeruli is due much more frequently to diffuse than to nodular lesions.

The diffuse lesions. Diffuse intercapillary lesions were apparently first described by Laipply and associates[9] under the designation of "focal fibrosis"; but these authors invalidated their observations by the inclusion of minimal alterations which may be found in normal glomeruli. A majority of investigators either ignore the diffuse lesions or state that they are not specific for diabetes. They are sometimes interpreted as an early stage of the nodular type, but a diffuse lesion may progress to complete obliteration of a glomerulus without the formation of definite nodules (Figure 8). Furthermore the complete Kimmelstiel-Wilson syndrome may develop in cases with diffuse lesions, in which

TABLE 4

Summary of data on diabetics 20 to 30 years of age.

Serial No.	Age-years	Sex	Duration-years	Proteinuria	Edema	Blood pressure mm. hg.	Retinitis	Renal insufficiency	Arterioles	Nodular lesions	Diffuse lesions	Hyaline glomeruli-%
1*	27	M	?	2	3	190/140	—	+	3	3	3	80
2	29	F	10	2	3	180/96	+	0	3	0	1	5
3	23	F	12	3	3	200/108	++	+	3	2	2	40
4	26	F	21	3	3	206/114	+	+	4	0	3	50
5**	26	F	14	3	0	224/150	—	+	3	1—	3	50
6	28	M	23	3	1	130/100	+	0	3	0	2	30
7	28	M	16	3	3	240/120	+	+	3	3	3	60
8	28	F	19	2	3	220/105	+	+	3	0	3	40

*The total plasma proteins were 5.7 gm. in Case 1.
**The total plasma proteins were 4.9 gm. in Case 5.

nodules are minimal or entirely absent (Tables 4 and 5). The clinical symptoms are related to the severity of the glomerular lesion but not to its histological type.

An early stage of diffuse intercapillary glomerulosclerosis is shown under low magnification in Figure 6. There is a convincing thickening and hyalinization of the intercapillary septa. In this study intercapillary sclerosis was not diagnosed when the changes were less conspicuous than those shown in Figure 6.

In Figure 7 a somewhat more advanced diffuse lesion

FIGURE 7 Glomerulus with well advanced diffuse intercapillary glomerulosclerosis. The hyaline afferent arteriole is shown.

FIGURE 8 Glomerulus with severe diffuse intercapillary glomerulosclerosis. The hyaline afferent arteriole is shown.

TABLE 5

Summary of data on diabetics 30 to 40 Years of Age. C Indicates cataract which obscured the retina.

Serial No.	Age-years	Sex	Duration-years	Proteinuria	Edema	Blood pres. mm. hg.	Retinitis	Renal insufficiency	Arterioles	Nodular lesions	Diffuse lesions	Hyaline glomeruli-%	Total plasma proteins. gm.
1	33	M	15	1	3	130/110	+	+	3	0	3	50	—
2	38	F	9	1—	1	124/74	0	0	3	0	1	5	—
3	33	M	10	1	0	122/80	0	0	3	1	2	10	—
4	39	F	1+	1	0	—	0	0	3	0	1	10	—
5	31	M	15	2	3	200/110	+	+	4	0	3	90	6.9
6	33	F	20	3	3	204/130	+	+	4	3	3	90	6.9
7	30	M	17	4	3	180/122	+	+	4	2	3	50	5.0
8	37	M	13.5	3	2	182/124	+	+	3	1	3	50	5.2
9	31	M	12	1	2	190/110	+	+	4	1—	1	90	—
10	30	F	16	1—	0	98/80	0	0	3	0	1	0	—
11	37	M	15	2	3	200/120	+	+	3	1	3	30	4.2
12	39	F	22	1	0	180/98	+	0	3	0	1	0	—
13	36	M	20	3	4	190/95	—	+	3	1	3	80	5.5
14	30	M	17	2	1	200/125	+	+	4	0	3	90	—
15	33	M	15	—	0	—	—	0	3	0	2	0	—
16	33	M	21	2	0	205/125	+	+	4	0	3	90	—
17	30	M	18	2	2	180/100	+	+	4	2	2	90	5.4
18	33	M	13	1	2	170/110	+	+	4	3	1	50	6.1
19	32	F	28	2	0	130/80	C	0	3	1	3	10	—
20	31	M	19	1	2	160/60	C	+	3	0	3	80	6.2

is shown. The afferent arteriole shows a thick layer of subintimal hyalin. Figure 8 illustrates a severe diffuse lesion in which there are only faint suggestions of nodules. The hyaline afferent arteriole may be seen.

PATHOGENESIS OF INTERCAPILLARY LESIONS

To study the development of the glomerular lesions the pathologist must have thin sections stained with azocarmine (Mallory-Heidenhain) or with the periodic acid-Schiff technic (McManus). A normal glomerulus is shown under low magnification in Figure 9. The dark linear masses in the central portions of the lobules are the inner basement membranes of the capillaries which are in close contact. Figure 9 should be compared with Figure 6 which shows an accumulation of hyalin between the inner basement membranes. A single lobule from Figure 9 is shown under high magnification in Figure 10. The individual capillaries are distinct and it may be seen that the intercapillary spaces are occupied by the cytoplasm of the glomerular epithelium. The occasional nuclei between the capillaries belong to the glomerular epithelium. The capillaries are embedded in a syncytium of glomerular epithelium.

The supporting tissue between the capillaries is called "mesangium" by those investigators who regard it as connective tissue; but collagenous fibers have not been demonstrated in the intercapillary spaces.

An early stage of a diffuse intercapillary lesion is shown in Figure 11. The capillaries are separated by a

FIGURE 9 Normal glomerulus showing thin intercapillary septa composed of the adjacent basement membranes.

FIGURE 10 High magnification of a lobule from Figure 9, showing the intercapillary space which is occupied by glomerular epithelial cells.

structureless hyaline mass and the inner basement membranes are no longer demonstrable. A constant feature of all intercapillary lesions is an increase of epithelial nuclei between the capillaries (Figures 4 and 11). Nuclei are seen only in the peripheral portions of large nodular lesions (Figure 4).

The origin of the intercapillary hyalin masses is difficult to determine. Kimmelstiel and Wilson[8] regarded the process as hyalinization of pre-existing collagenous fibers. Allen[10] believes that the hyalin is derived from thickening and splitting of the inner capillary basement membranes, and therefore regards the lesion as intramural rather than intercapillary. I have also supported this interpretation[11]. McGregor[12] demonstrated that the intercapillary lesions of chronic glomerulonephritis are derived from the inner capillary basement membranes.

However, McManus[7] believes that the hyalin is deposited in the intercapillary spaces and not derived from basement membranes since it is chemically different from them. By the use of phase microscopy Churg and Grisham[13] concluded that the hyalin is deposited beneath intact basement membranes. According to this concept the hyalin may be an albuminoid substance deposited from the blood, and in this respect similar to arteriolar hyalin.

Neither of these interpretations affords an adequate explanation of the great increase of epithelial nuclei in the intercapillary spaces that accompanies the accumulation of hyalin.

The distinction between the intercapillary lesions of diabetes and those of chronic glomerulonephritis. In rare instances of chronic glomerulonephritis nodular lesions are found that are similar to those of diabetes (Figure 5), and a high percentage of cases of this disease show diffuse intercapillary sclerosis (Figure 12). This fact is responsible for the widespread opinion that a diagnosis of diabetes cannot be established on the basis of diffuse lesions alone. It is true that one must exclude chronic glomerulonephritis before making a diagnosis of diabetes on the basis of either form of intercapillary glomerulosclerosis, and especially when only diffuse lesions are present; but this can usually be done without difficulty. In diabetes there is invariably more or less hyaline in the afferent arteriole in association with an intercapillary lesion while this change is rarely seen in chronic glomerulonephritis. Also the study of a number of glomeruli will usually reveal some with convincing intracapillary glomerulonephritis. In the earlier stages the intercapillary lesions of glomerulonephritis have a fibrillar structure. Intercapillary lesions do

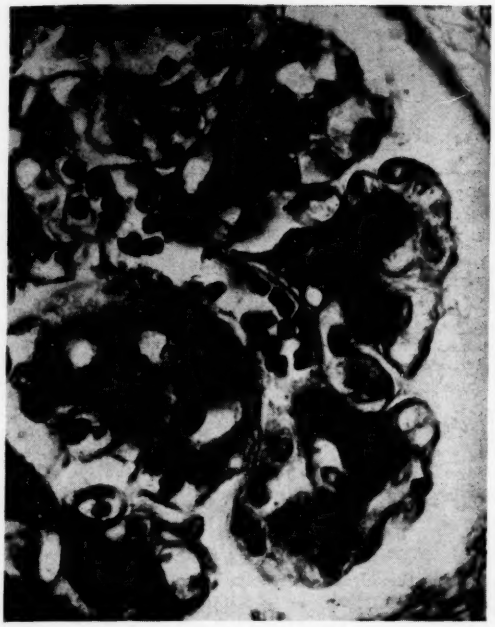

FIGURE 11 Glomerulus showing an early stage of diffuse intercapillary glomerulosclerosis. Note disappearance of internal basement membranes and an increase in nuclei in the intercapillary hyaline masses.

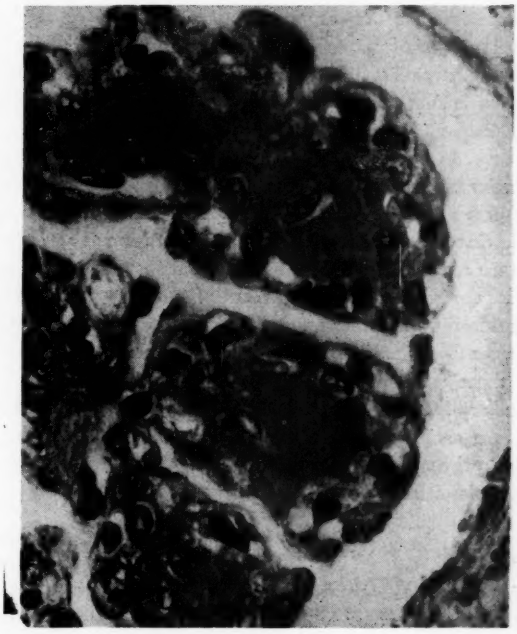

FIGURE 12 Chronic glomerulonephritis. Glomerulus showing diffuse intercapillary glomerulosclerosis.

not develop in primary hypertension. When chronic glomerulonephritis has been excluded, diffuse intercapillary sclerosis is highly specific for diabetes.

The frequency of intercapillary lesions. Some data are available with respect to the frequency of nodular lesions. Henderson[14] found nodular lesions in 19.5 per cent of 313 diabetics, and Kimmelstiel and Porter[15] give the incidence as about 17 per cent. The incidence of nodular and diffuse lesions in the 1465 diabetics of my series is shown in Table 6. Nodular lesions, practically all of which were associated with diffuse lesions, were found in 12.8 per cent of 688 males and 19.4 per cent of 777 females. When those showing only diffuse lesions are included, the total incidence of intercapillary sclerosis was 19.5 per cent for the males and 30 per cent for the females. No intercapillary lesions were found in subjects under 20 years of age, but this group is small. In subjects over 50 years of age both nodular and diffuse lesions are about twice as frequent in females as in males. It will be noted that the number of diagnoses of diabetes is increased about 50 per cent by inclusion of the diffuse lesions.

TABLE 6

Incidence of nodular and diffuse intercapillary lesions with respect to age and sex

Sex and Age at death	No. of diabetics	Nodular and diffuse lesions %	Diffuse lesions only %	total intercapillary %
0-20 yrs. Males	16	0.0	0.0	0.0
0-20 yrs. Females	17	0.0	0.0	0.0
20-50 yrs. Males	108	22.2	9.3	31.5
20-50 yrs. Females	126	8.7	9.5	18.2
50-90 yrs. Males	564	11.3	6.4	17.7
50-90 yrs. Females	634	22.1	11.0	33.1
Total Male	688	12.8	6.7	19.5
Total Female	777	19.4	10.6	30.0

Relation of intercapillary sclerosis to the duration of diabetes. Both nodular and diffuse lesions are included in Table 7. The duration of the diabetes has a striking influence on the development of intercapillary glomerulosclerosis in the younger diabetics—only 3 per cent of those under 40 years of age showing the lesion with less than 10 years of diabetes. It has been reported frequently by clinicians that juvenile diabetics seldom develop renal disease with less than 10 years of diabetes, but after a decade or more of the disease renal symptoms and signs are very common. In the older age groups the influence of duration is definite but less pronounced.

The influence of the duration of diabetes on the development of glomerular lesions is brought out in another way in Table 8, in which the duration of the disease is shown in subjects with intercapillary lesions.

Relation of intercapillary glomerulosclerosis to hypertension. In Table 9 it is seen that intercapillary glomerulosclerosis has a causal relation to hypertension in subjects under 50 years of age. It appears highly probable that in juvenile diabetes the hypertension is caused by the renal lesion.

In the subjects over 50 years of age, however, the relationship is not clear. Intercapillary lesions develop frequently in nonhypertensive subjects, and two-thirds of those with severe hypertension do not have intercapillary lesions. This situation may be partly explained on the assumption that many of the older individuals have primary hypertension as well as diabetes. Possibly arteriolosclerosis alone may cause hypertension.

PROTEINURIA IN DIABETES

In my series satisfactory qualitative examinations for proteinuria were made at the last hospital admission in 897 cases, but few quantitative studies are available. Proteinuria was absent in 21 per cent, a trace to 1 plus in 47 per cent, and over 1 plus in 32 per cent. The incidence of intercapillary lesions with different degrees of proteinuria is shown in Table 10. The frequency of glomerular lesions increases with the severity of the proteinuria, and 61 per cent of the subjects under 60 years of age with moderate to severe proteinuria had intercapillary lesions. But the absence of proteinuria does not exclude an intercapillary lesion.

Over one-half of the subjects over 60 years of age with moderate to severe proteinuria did not have glomerular lesions. In about one-third of this group the proteinuria may be explained as a result of cardiac failure, but there remains a large number with neither glomerular lesions nor cardiac failure. It appears that disease of the arteries and arterioles may cause proteinuria. Moderate to severe proteinuria is suggestive of the presence of glomerular lesions in persons under 60 years of age, but does not constitute proof that such lesions are present.

In subjects with intercapillary glomerulosclerosis the available data show that all of those under 50 years of age had proteinuria, including those with only mild diffuse lesions. The proteinuria was mild in 12 and moderate to severe in 35 cases. In subjects over 50 years of age, proteinuria was absent in 27, mild in 90 and moderate to severe in 103 cases. There was less protein in those with only mild diffuse lesions, but otherwise

TABLE 7

Relation of intercapillary glomerulosclerosis to the duration of diabetes

Age at Death	Total diabetic	Less than 10 yrs			10 to 20 yrs			Over 20 yrs		
		Total No.	+ No.	+ %	Total No.	+ No.	+ %	Total No.	+ No.	+ %
20-40 yrs	108	66	2	3.0	35	18	51.4	7	7	100
40-60 yrs	348	253	50	19.8	72	30	41.7	23	15	65.0
60-90 yrs	787	551	112	20.3	178	65	36.5	58	24	41.4

TABLE 8

Distribution of 369 cases of intercapillary glomerulosclerosis with respect to the age at death and the duration of the diabetes.

Age at Death	No. of Cases of intercap. sclerosis	Duration under 10 yrs. %	Duration 10 to 20 yrs. %	Duration over 20 yrs. %	Duration indefinite yrs. %
20-40 yrs	28	7	64	25	4
40-60 yrs	105	48	28	14	9
60-90 yrs	236	47	28	10	15

TABLE 9

Relation of intercapillary sclerosis to hypertension

Age at Death	Total diabetic	Blood pressure below 150/90 mm. Hg.		Blood pressure 150 to 179/90 mm. Hg.		Blood pressure 180/90 mm. Hg. and Higher	
		No.	%+*	No.	%+	No.	%+
10-30 years	44	31	0.0	5	0.0	8	100.0
30-50 years	124	70	14.3	13	46.1	41	73.1
50-90 years	955	380	22.1	279	25.8	296	37.1

*% + Indicates the percentage with intercapillary sclerosis

TABLE 10

The relation of proteinuria to intercapillary glomerulosclerosis

Proteinuria Age at Death	None Number	% +	Mild *Number	0 +	Moderate to severe Number	0 +
0-60 years	58	10	118	24	120	61
60-90 years	134	19	300	23	167	46

*% + Indicates the percentage with intercapillary lesions.

TABLE 11

Relation of edema to intercapillary glomerulosclerosis

Age of Death	Total Diabetics	No edema No.	* + %	Mild edema No.	+ %	Moderate and severe edema No.	+ %
10-30 yrs.	69	59	1.7	3	33.3	7	85.7
30-50 yrs.	186	133	15.0	19	42.1	34	70.6
50-90 yrs.	1192	879	24.1	189	28.5	124	36.3

*% + Indicates the percentage with intercapillary lesions

there is no good correlation between the amount of protein and the severity of the glomerular lesions. Rifkin and associates[16] have noted this lack of correlation.

The relation of edema to intercapillary glomerulosclerosis. In Table 11 it is shown that diabetics under 30 years of age without edema rarely have glomerular lesions, but if they have moderate to severe edema such lesions are probably present. In the group 30 to 50 years of age the glomerular lesions may be present without edema, but a fairly severe edema is a good indication of glomerulosclerosis. However, in the group over 50 years of age there is little correlation between edema and intercapillary lesions.

The clinical data and the autopsy observations were carefully reviewed in all of the diabetics who had edema of any degree. All of those showing intercapillary glomerulosclerosis were classified as renal edema. Those with clinical and postmortem evidence of cardiac failure without intercapillary glomerulosclerosis were classified as cardiac edema. There is some overlapping of the renal and cardiac groups in the older diabetics since many had both intercapillary lesions and cardiac failure. It will be noted that renal disease is more frequently the cause of the edema in the younger than in the older diabetics, and that in diabetics past 60 years of age cardiac edema is twice as frequent as the renal form (Table 12).

There remain 132 subjects with edema who had neither renal lesions nor cardiac disease. The edema in this group was usually mild but occasionally severe. In 40 of these the edema was limited to the lower extremities and associated with gangrene or thrombophlebitis. There were 12 cases presumably due to the associated cirrhosis of the liver. Nineteen subjects with mild edema were emaciated and the edema may have been on a nutritional basis. In the remaining 61 cases no adequate explanation of the edema was available.

The frequency of edema as associated with intercapillary glomerulosclerosis is shown in Table 13. About two-thirds of those under 50 years of age showed some degree of edema. Edema was about as frequent in those with diffuse lesions only as in those with nodular and diffuse lesions. In the group over 50 years of age edema of some degree was present in 37.7 per cent of those with nodular and diffuse lesions and 16 per cent of those with diffuse lesions only. The absence of edema, therefore, by no means excludes the presence of glomerular lesions.

The plasma proteins. In diabetics with glomerular lesions there is usually a continuous loss of protein in the urine which depletes the plasma proteins. Malnutrition, when present, also tends to cause hypoproteinemia. The plasma proteins were determined in 57 subjects with intercapillary glomerulosclerosis. The relation of the total protein level to edema is as follows: Total protein 3.5 to 4.9 gm. per cent, edema in 6 of 7 cases; 5.0 to 5.9 gm., edema in 18 of 22 cases; 6.0 to 6.9 gm., edema in 15 of 19 cases; 7.0 to 8 gm., edema in 1 of 9 cases. There is usually some degree of hypoproteinemia, and edema was present in 39 of 48 subjects with a total protein of less than 7 gm. per cent. There is, however, no close correlation between the degree of edema and the severity of the hypoproteinemia. My observations are in accord with those of Rifkin and associates[12].

Diabetics with both edema and hypertension. In Table 14 the cases are arranged with respect to the degree of edema and the presence or absence of hypertension. It appears that intercapillary glomerulosclerosis is much more frequent in hypertensive than nonhypertensive edematous subjects. In a diabetic below 60 years of age the presence of both edema and hypertension makes the diagnosis of intercapillary glomerulosclerosis highly probable. Hypertension is more important than edema in the diagnosis of intercapillary glomerulosclerosis in persons under 60 years of age.

TABLE 12

Diabetics with edema arranged with respect to the probable cause of the edema.

	No. of Diabetics	No. with edema	Renal edema	Cardiac edema	Other forms of edema
Age at Death					
0-20 years	34	0	0	0	0
20-40 years	131	34	21	3	10
40-60 years	435	104	49	31	24
60-90 years	1011	265	52	115	98
Total	1611	403	122	149	132

TABLE 13

Incidence of edema in association with intercapillary Glomerulosclerosis

	Nodular and diffuse lesions		Diffuse lesions only	
Age at Death	No. of cases	% with edema	No. of cases	% with edema
20-50 years	33	66.7	23	61
50-90 years	204	37.7	101	16

THE KIMMELSTIEL-WILSON SYNDROME

The Kimmelstiel-Wilson syndrome, as originally described, referred to a diabetic with severe proteinuria and severe edema of renal origin. The clinical features

were attributed to the glomerular lesions which permitted a loss of protein in the urine with consequent depletion of the plasma proteins and edema. Because of the resemblance to lipoid nephrosis this clinical picture is often called the nephrotic syndrome. Edema in a diabetic is often regarded as evidence of intercapillary glomerulosclerosis, but it was pointed out in connection with Table 10 that in the older diabetics edema is more frequently due to cardiac failure and other causes than to a renal lesion.

In Table 15 the incidence of edema, grades 2+ to 4+ is shown in all the cases of intercapillary glomerulosclerosis. All of the subjects under 50 years of age had some degree of proteinuria, but 23 of those beyond that age had no protein in the urine at the last hospital admission. If we make a very liberal interpretation of the nephrotic syndrome and ignore the amount of protein in the urine, such a syndrome occurred in 52.6 per cent of the younger diabetics and 18.1 per cent of those over 50 years of age, with intercapillary glomerulosclerosis. If we adopt a more rigid definition of the nephrotic syndrome requiring at least 2+ proteinuria and 2+ edema, the percentages become 45.6 and 14.9 respectively for those below and above the age of 50 years. It is noteworthy that the nephrotic syndrome is much more frequent in younger than in older diabetics.

Rogers and Robbins[17] found that intercapillary glomerulosclerosis is not a clear-cut entity. The glomerular lesions are often absent in a diabetic with the nephrotic syndrome, and conversely the glomerular lesions are frequently found in the absence of the nephrotic syndrome.

The incidence of intercapillary glomerulosclerosis in diabetics with and without edema is shown in Table 11. It appears that moderate to severe edema in a diabetic under 50 years of age is strongly suggestive of intercapillary glomerulosclerosis; but in the older diabetics it is a much less important diagnostic sign. This is due in part at least to the frequent presence of cardiac edema in elderly diabetics.

It may be objected that my observations are weakened by the inclusion of diffuse intercapillary lesions in which no nodules were present. In Table 4 three cases are shown, numbers 2, 4, and 8, in which the complete nephrotic syndrome developed in the absence of any nodular lesions. In Table 5 there is one complete nephrotic syndrome, case 5, without nodular lesions. The symptoms are usually related to the severity of the glomerular lesions and not to the histological type.

It may be concluded that intercapillary glomerulosclerosis is not a distinct entity in the sense that it regularly produces a recognizable clinical syndrome. In fact only 20 per cent of the 339 cases of intercapillary glomerulosclerosis in this series had a complete nephrotic syndrome (Table 15). It is also true that in the older diabetics edema and proteinuria due to cardiac failure may simulate the nephrotic syndrome.

The clinical signs of renal disease in diabetes. In a diabetic with demonstrable renal insufficiency the clinician may be reasonably sure that intercapillary glomerulosclerosis is present after he has excluded pyelonephritis and hydronephrosis. Before the development of renal insufficiency the specific glomerular lesion is sug-

TABLE 14

Incidence of intercapillary glomerulosclerosis in subjects with edema, with and without hypertension

Age at Death	Mild edema				Moderate and severe edema			
	With hypertension		Without hypertension		With hypertension		Without hypertension	
	No. of Cases	*% +	No. of Cases	% +	No. of Cases	% +	No. of Cases	% +
20-60 years	23	78.3	31	6.4	54	83.3	20	15.0
60-90 years	82	30.7	58	8.6	77	37.7	20	15.0

*% + Indicates the per cent with intercapillary lesions.

TABLE 15

Incidence of moderate and severe edema in association with intercapillary glomerulosclerosis

Age at death	No. of cases	No. with edema Grades 2 to 4	No. with complete nephrotic syndrome
20-30 years	8	6	6
30-40 years	20	11	9
40-50 years	29	13	11
50-60 years	69	19	21
60-70 years	132	25	19
70-90 years	81	7	2
20-50 years	57	30 (52.6%)	26 (45.6)
50-90 years	282	51 (18.1%)	42 (14.9)
Total	339	81 (23.9%)	68 (20.0)

TABLE 16

Incidence of renal insufficiency in diabetics with intercapillary glomerulosclerosis with respect to age at death

Age at Death	No. with intercapillary lesions	No. without renal insufficiency	No. with renal insufficiency
20-30 years	8	2	6
30-40 years	20	6	14
40-50 years	29	13	16
50-60 years	72	47	25
60-70 years	132	98	34
70-90 years	104	83	21
20-50 years	57	21	36(63%)
50-90 years	308	228	80(26%)

gested in diabetics under 50 years of age, by the presence of hypertension or severe edema of renal origin. In the older diabetics the only convincing evidence of intercapillary sclerosis is renal insufficiency not due to pyeloephritis or hydronephrosis, but a severe edema of renal origin may be sufficient to establish the diagnosis.

RENAL INSUFFICIENCY

In Table 16 all the cases of intercapillary glomerulosclerosis are arranged with respect to age and the presence or absence of renal insufficiency at the time of death. Over 90 per cent of those with renal insufficiency died of uremia; in the others renal failure was a contributory cause of death. It is noteworthy that the percentage dying of uremia decreases with age. It is high in those under 50, but low in the older subjects.

In this group of 1945 diabetics there were 119 subjects with renal insufficiency on a vascular basis. Three of these were examples of malignant hypertension with no specific diabetic lesions, but all the rest showed diabetic glomerular lesions which were at least in part responsible for the destruction of the glomeruli.

On microscopic examination the diabetic kidney with uremia shows extensive tubular atrophy which is due chiefly to obstruction of the glomeruli. Usually from 50 to 90 per cent of the glomeruli are completely hyalinized. When followed through successive stages it may be seen that occlusion of the glomerular circulation is due largely to progressive increase of the intercapillary lesions or to occlusion of the afferent arterioles. Presumably the narrowing of the large and small renal arteries increases the ischemia and promotes the cortical atrophy. The hyaline glomeruli are usually much larger than those of primary hypertension, and frequently they are surrounded by fibrous epithelial crescents as they are in primary hypertension and chronic glomerulonephritis. The presence or absence of fibrous crescents does not help in the differentiation of these three forms of renal atrophy.

The hyaline glomeruli in diabetic kidneys occasionally contain *acidophilic hyaline masses* which are stained a bright red by azocarmine when the stain is so adjusted that the arteriolar hyalin is red. Koss[18] has called particular attention to these lesions and shown that they give the staining reactions of fibrinoid. Usually only an occasional hyaline glomerulus is affected; rarely the lesions are extensive. Frequently the acidophilic mass is crescent shaped and occupies the periphery of a glomerular lobule (Figure 13). At first sight, the lesion appears to be a capillary thrombosis, but careful study reveals it to be intercapillary in position. The acidophilic

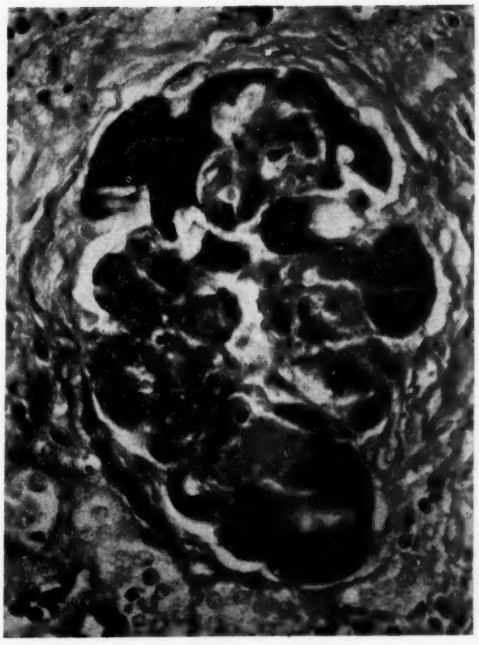

FIGURE 13 Hyaline glomerulus from a diabetic, showing acidophilic hyaline masses.

masses appear to be derived from intercapillary hyaline lesions which expand and become acidophilic. Nearly 90 per cent of the diabetic kidneys of this series, which had progressed to renal insufficiency, showed at least an occasional acidophilic mass in a hyaline glomerulus. I am in agreement with Koss[17] that this lesion is encountered much more frequently in diabetics than in nondiabetics.

The diabetic kidney with renal insufficiency must be distinguished from chronic glomerulonephritis and primary hypertension with renal insufficiency.

(a) In chronic glomerulonephritis the intercapillary proliferation closes the glomerular capillaries and tubular atrophy results. There is rarely any hyalin in the afferent glomerular arterioles.

(b) In primary hypertension with uremia the atrophy is caused chiefly by occlusion of the small renal arteries. Arteriolosclerosis is usually inconspicuous and there are no primary glomerular lesions. The hyaline glomeruli are small.

(c) In the diabetic kidney with uremia the glomeruli are destroyed by intercapillary sclerosis and by severe hyalinization of the afferent arterioles. Frequently sclerosis of the arteries contributes to the atrophy. In the persisting glomeruli intercapillary sclerosis may be seen,

and it may be possible to recognize nodular lesions in the hyaline glomeruli. The demonstration of acidophilic masses in hyaline glomeruli also supports the diagnosis of diabetes.

Since primary hypertension is so frequent in elderly diabetics one would expect to find a number of cases of malignant hypertension among the subjects with uremia. But there were only 3 cases of malignant hypertension among 119 cases of uremia. These 3 cases showed no diabetic glomerular lesions and the cortical atrophy was caused by occlusion of the small renal arteries, not by arteriolar or glomerular lesions.

The relation of arteriolosclerosis to intercapillary glomerulosclerosis. More or less hyalinization of the afferent glomerular arteriole is invariably found in association with an intercapillary glomerular lesion, even those of a mild diffuse type. The hyalinization of the arteriole develops concomitantly with the glomerular lesion, but the severity of the process in the arteriole does not correspond closely with the intensity of the lesion in the glomerulus. The arteriolar lesion does not cause the intercapillary changes but it may totally obstruct the blood supply and bring hyalinization of the glomerulus. A hyaline arteriole is an essential feature of the diagnosis of intercapillary glomerulosclerosis.

Tables 4 and 5 summarize the more important data on diabetics with intercapillary glomerulosclerosis between the ages of 20 and 30 years, and 30 and 40 years respectively. The difficulty of defining the nephrotic syndrome is apparent. Retinitis is usually but not invariably associated with renal insufficiency. In these younger subjects arteriolosclerosis is invariably severe. It will be noted that diffuse lesions are always present and nodular lesions frequently absent. The complete nephrotic syndrome may develop in the absence of nodular lesions (Numbers 2, 4, 8, Table 15; Number 5, Table 16).

SUMMARY

This report is based upon a microscopic study of the kidneys of 1465 diabetic subjects.

Arteriolosclerosis is more frequent and more severe in diabetes than in primary hypertension. It was found in about one-half of the subjects between the ages of 20 and 50 years, and in nearly two-thirds of those past the age of 50 years. The highest incidence is in elderly females. It is not due to hypertension since it was found in over one-half of elderly nonhypertensive diabetics. It appears to be caused by the diabetic state, and in young diabetics it is largely responsible for the development of hypertension. Arteriolosclerosis increases in frequency with the duration of the diabetes, especially in the young subjects.

Hypertension (150/90 mm. Hg. or higher) was present in 60.9 per cent of 455 diabetic males and 67.8 per cent of 516 diabetic females over 50 years of age. The incidence of hypertension in diabetic males is about 50 per cent greater than in nondiabetic males, and about 20 per cent greater in diabetic than in nondiabetic females over 50 years of age. Presumably the hypertension of elderly diabetics is chiefly of the primary type, that is, a majority of the cases represent an accidental association of diabetes and primary hypertension.

We may distinguish a "nodular" and a "diffuse" type of intercapillary glomerulosclerosis. Nodular lesions are always associated with diffuse lesions, but in about one-third of the cases only diffuse lesions are found. Nodular lesions develop from diffuse lesions and no sharp separation between the two types can be made. The recognition of the diffuse lesions increases by about 50 per cent the number of positive diagnoses of diabetes that can be made by study of the kidneys. The destruction of glomeruli is due much more frequently to diffuse than to nodular lesions. The clinical symptoms bear some relation to the intensity of the glomerular lesions but not to their histological type. The complete nephrotic syndrome may develop when only diffuse lesions are present.

In chronic glomerulonephritis, intercapillary lesions of the nodular type are very rare but the diffuse type is very common. A distinction between the intercapillary lesions of chronic glomerulonephritis and diabetes can be made without difficulty. In nephritis there is rarely any hyaline in the afferent arterioles and the intercapillary lesions are evenly distributed through the glomerulus. In diabetes there is always some hyalinization of the afferent arteriole and the intercapillary lesions are variable in size and shape. When chronic glomerulonephritis has been excluded the diffuse lesions are as specific for diabetes as the nodules.

Nodular intercapillary lesions were found in 12.4 per cent of 688 diabetic males and 19.4 per cent of 777 diabetic females. When the diffuse lesions are included the total incidence of intercapillary glomerulosclerosis is 19.5 per cent for males and 30 per cent for females. The frequency of intercapillary lesions increases with the duration of diabetes, especially in younger subjects.

In diabetics under 50 years of age intercapillary lesions are much more frequent in hypertensive subjects, but after that age the relation to hypertension is much less prominent.

Intercapillary lesions may be present when proteinuria is mild or completely absent, but a severe proteinuria suggests the presence of the glomerular lesions, especially in younger diabetics.

Severe edema in a diabetic under 50 years of age is usually of renal origin and strongly suggests the presence of intercapillary glomerulosclerosis, but in the older diabetics edema is of much less diagnostic value with respect to the presence of a renal lesion since it is usually due to cardiac failure or other causes.

The nephrotic syndrome, rigidly defined as proteinuria 2+ or more and edema 2+ or greater, developed in 45.6 per cent of 57 cases of intercapillary glomerulosclerosis in subjects under 50 years of age, and in 14.9 of those beyond that age. Intercapillary glomerulosclerosis is therefore not a distinct entity in the sense that it usually produces a recognizable clinical syndrome.

Renal insufficiency, usually clinical uremia, developed in 63 per cent of the subjects with intercapillary glomerulosclerosis under 50 years of age and in 26 per cent of those beyond that age. Renal insufficiency in a diabetic is due chiefly to arteriolosclerosis and intercapillary glomerulosclerosis. Renal insufficiency in primary hypertension is due largely to obstruction of the small renal arteries—primary glomerular lesions being absent and arteriolosclerosis inconspicuous.

A clinical diagnosis of intercapillary glomerulosclerosis may be made with reasonable certainty in any diabetic by the demonstration of renal insufficiency not due to pyelonephritis or hydronephrosis. In diabetics under 50 years of age the presence of intercapillary glomerulosclerosis is strongly indicated by severe proteinuria, severe edema, hypertension or retinitis; but after the age of 50 years these symptoms and signs have much less diagnostic significance.

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DISCUSSION

SHIELDS WARREN, M.D. (*Boston*): Doctor Bell has pointed out the histologic characteristics of renal lesions. The different types of hyaline lesions in the kidney glomerulus may be differentiated from one another by another means. (Slides were shown to demonstrate pictures taken using the polaroid ultraviolet color translation microscope and setting the apparatus to obtain specific absorption bands in the ultraviolet range; these pictures were taken with the 280 band represented in blue, and 263 band in green, and a 248 band in red).

The first picture represents a portion of a normal renal glomerulus. There is relatively little there to see. One can make out the outlines of the capillary loops and the typical structure. In contrast, in the second picture one can see a diabetic glomerulus. The hyaline masses present have quite different absorption characteristics from the normal. In the third picture, showing an ordinary type of glomerular sclerosis, one can see a marked difference in the color of the hyaline material, indicating ultraviolet absorption different from the normal and the diabetic glomerulus.

It is too early to be able to tell with any degree of certainty by this means the nature of these materials, but it is of interest that another type of technic from that used by Doctor Bell serves to reenforce his point.

ABSTRACTS

Abaza, A.; Varroud-Vial, J.; and Rombauts, M. (*Hopital Villeneuve-Saint-Georges, Paris, France*): YOUNG'S SYNDROME. La presse medicale *61*:495, April 1, 1953.

Referring to two personal cases, the authors suggest the term "Young's Syndrome" for the clinical picture including: late statural growth; acquired obesity during pregnancy accompanied by a high incidence of fetal or neonatal mortality or in birth of babies weighing more than 4 kg.; hyperlactation; late occurrence, often postmenopausal, of diabetes mellitus; and hereditary tendency to diabetes frequently traced up and down in the ascending and descending line. This clinical syndrome appears to reproduce such effects as observed by Young in experimental animals following injection of pituitary somatotropic hormone.

Abraham, S.; and Chaikoff, I. L. (*Div. of Physiol. of Univ. of California Sch. of Med., Berkeley, Calif.*): LABELING OF SPECIFIC GLUCOSE CARBONS FORMED FROM SUCCINIC ACID-1-C^{14} AND -2-C^{14} IN THE DIABETIC DOG. Arch. Biochem. *41*:143-47, November 1952.

Samples of urinary glucose obtained from diabetic dogs that had been injected with succinic acid-1-C^{14} and succinic acid-2-C^{14} were degraded, and the C^{14} content of individual glucose carbons was determined. In the experiment with succinic acid-1-C^{14}, C^{14} activity was found in only the two middle carbons of the urinary glucose. When succinic acid-2-C^{14} was injected, 80 per cent of the C^{14} found in the glucose molecule resided in carbons 1, 2, 5, and 6. These labeling patterns are discussed in connection with the conversion of palmitic acid to glucose.

Amatuzio, Donald S.; Stutzman, Francis L.; Vanderbilt, Muriel J.; and Nesbitt, Samuel (*Vet. Admin. Hosp. and Univ. of Minn. Med. Sch., Minneapolis, Minn.*): INTERPRETATION OF THE RAPID INTRAVENOUS GLUCOSE TOLERANCE TEST IN NORMAL INDIVIDUALS AND IN MILD DIABETES MELLITUS. J. Clin. Investigation *32*:428-35, May 1953.

A study has been made of the rapid intravenous glucose tolerance test by following the disappearance rate of glucose. It was found that the rate of removal in the normal individual maintained on an adequate carbohydrate diet remained constant on repeated tests and was independent of the dose administered for each subject.

By determining the removal rate, a sharp separation was found between the patients with known mild diabetes (26), severe diabetes (13) and the group of normal controls (70). A decreased rate of removal has been observed in other conditions, including obesity unrelated to a family history of diabetes, inflammatory disease, uremia, weight loss due to diet, and decompensated portal cirrhosis.

Barford, Bent. (*Chemical-Biological Lab., "Medicinalco" Ltd., Copenhagen, Denmark*): GLUCONEOGENESIS FROM OLEIC ACID IN THE PERFUSED CAT'S LIVER. Acta physiologica Scandinavica *28*:41-59, March 31, 1953.

Cats' livers were perfused by the addition of an emulsion of glycerol trioleate to the perfusion blood. Before the fat addition, during the perfusion and at the end of the experiment, samples of the blood and the liver were taken for determination of glucose, glycogen, lactic acid, fat, ketone bodies and urea. In four of seven experiments, there was a formation of carbohydrate which exceeded the maximum amount which could be formed from the metabolized protein and the glycerol part of the fat. At the same time, there was a decrease of the fatty acids. It is suggested that oleic acid was the source of carbohydrate found in the experiments with added fat.

Beattie, J.; and Chambers, R. D. (*Strangeways Res. Lab., Cambridge*): CHANGES IN BLOOD GLUCOSE LEVELS AFTER HYPOTHALAMIC LESIONS. Quart. J. Exper. Physiol. *38*:87-89, May 1953.

Section of the efferent hypothalamic pathways to the brain stem produces a fall in resting blood glucose level of about 38 per cent below that of normal rats kept under the same experimental conditions. Injection of a standard dose of insulin produced, after 30 minutes,

the same fall in blood glucose concentration in rats with hypothalamic lesions as in normal animals.

Beatty, Clarissa H. (*Dept. of Biochemistry of Oregon Med. Sch., Portland, Ore.*): LEVELS OF ERGOTHIONEINE IN THE RED BLOOD CELLS IN EXPERIMENTAL DIABETES. J. Biol. Chem. *199*:553-61, December 1952.

The author found that values for ergothioneine and reduced glutathione of red blood cells increase as the rat matures. Glutathione levels of the red blood cell reach a plateau in rats at about 10 weeks of age and the ergothioneine at about 6 months of age. In rats 6 to 12 months old, two different kinds of stress, hemorrhage and fasting were shown to increase the ergothioneine levels of erythrocytes. However, the removal of 95 per cent or more of the pancreas produced a marked decrease in red blood cell ergothioneine. Rats with no intestinal pancreatic juice, owing to a sham operation, but with normal blood glucose levels showed no changes in red blood cell ergothioneine. However, when the pancreatic tissue surrounding the splenic blood supply was removed, the blood glucose rose and the red blood cell ergothioneine fell. The administration of insulin and hyperglycemic factor to depancreatized rats had no effect on ergothioneine concentrations in the red blood cell. The red blood cell values for reduced glutathione of both alloxan-diabetic and depancreatized rats were within the control range.

Bell, David M.; Burns, Thomas; and Schieve, James (*Dept. of Med., Duke Univ. Sch. of Med., Durham, N. C.*): DEMONSTRATION THAT INSULIN IS FIXED LOCALLY WHEN INJECTED INTO THE FEMORAL ARTERY IN HUMANS. Am. J. Med. *13*:641, November 1952 (Abstract of a paper presented at the Sixth Annual Meeting of the Southern Society for Clinical Research, Atlanta, Ga., January 19, 1952).

Small doses of insulin (1/80 unit per kg.) are reported to have produced definite, but small, asymptomatic depression of the blood sugar. Two groups of 10 hospital patients wee compared in their response to intravenous and intra-arterial insulin injection. It was noted that the blood sugar fell following intravenous injection; simultaneous femoral venous and arterial blood samples contained essentially the same sugar concentration. However, after femoral artery injection of insulin, there was an increase in the arteriovenous difference during the time of fall. A further experiment using seven healthy students was conducted in which insulin was given into the femoral artery and blood taken from the same artery and from the femoral vein of each leg. There was an increase in A-V sugar difference across the injected leg, with essentially no measurable difference across the control leg during the time of fall of arterial concentration. At 15 minutes (the point of maximum arterial drop), there was a statistically significant difference in A-V differences in both experiments. On the basis of these data, the authors suggest that insulin injected into a femoral artery is fixed in the extremity and that it increases the glucose removal from that extremity without corresponding increase in the opposite extremity.

Berkman, James; Rifkin, Harold; and Ross, George (*Montefiore Hosp., New York, N. Y.*): THE SERUM POLYSACCHARIDES IN DIABETIC PATIENTS WITH AND WITHOUT DEGENERATIVE VASCULAR DISEASE. J. Clin. Investigation *32*:415-21, May 1953.

The concentrations of total non-glucosamine polysaccharides bound to serum protein, serum glucosamine, the protein (tyrosine), and polysaccharide of serum mucoprotein are within normal limits in diabetic patients without clinically detectable degenerative vascular disease. In diabetic patients with degenerative vascular disease, the total polysaccharides bound to serum proteins and the glucosamine of the serum are increased. The values in such patients are not significantly influenced by the presence of renal involvement.

Bertino, J.; Dawson, N.; Greer, R.; Margen, S.; and Kinsell, L. W. (*Inst. for Metabolic Res., Highland Alameda County Hosp., Oakland, Calif.*): UTILIZATION OF INFUSED FRUCTOSE AND INVERT SUGAR IN HUMAN SUBJECTS. Am. J. Med. *13*:506, October 1952 (Abstract of paper read by title at the Western Sectional Meeting of the American Federation for Clinical Research in Carmel, Calif., January 24, 1952).

In eleven normal adult human subjects studied, the authors were able to confirm the recent reports that the infusion of invert sugar and of fructose to human subjects results in a lesser degree of hyperglycemia and glycosuria than when an equal amount of glucose is infused over the same period of time. Studies dealing with changes in serum phosphorous and with respiratory quotient designed to further evaluate the mechanisms involved will be reported.

Bockus, H. L.; Bogoch, A.; and Roth, J. L. A. (*Dept. of Gastroenterology and Gastro-Intestinal Res. Lab., Grad. Hosp. of Univ. of Penn. Grad. Sch. of Med., Philadelphia, Pa.*): ACUTE PANCREATITIS: DIAGNOSIS AND TREATMENT. South. M. J. *46*:388-96, April 1953.

The authors discuss etiologic factors, the differentiation between edema and necrosis, serum enzymes in diagnosis, complicating biliary tract disease, and therapy, based upon 33 cases studied during the decade, 1941-1951.

Bohan, Edward M.; Ackerman, Joseph L.; Hynes, Thomas V.; and Tarrant, Harold A. (*Dept. of Metabolism, St. Francis Hosp., Wilmington, Del.*): FURTHER OBSERVATIONS ON THE USE OF THE POST-PRANDIAL BLOOD SUGAR IN THE TREATMENT OF DIABETES MELLITUS: APPARENT CURE OF THREE OBESE DIABETICS. Delaware M. J. 25:108-14, May 1953.

The frequency of obesity occurring with diabetes is often underestimated. Nine out of ten diabetics, whose diabetes developed after the age of twenty, have had obesity before the onset of the disease. The probability of reducing the blood sugar to normal by weight reduction is illustrated by three cases.

Boldt, Martin H.; and Boldt, Shirley K. (*Louisville, Ky.*): A SIMPLIFIED APPROACH TO THE DIET THERAPY OF THE DIABETIC. J. Kentucky M. A. 50:462-67, November 1952.

A simplified method of dietary instruction to the diabetic is presented. The similarity between a diabetic diet and one for a comparable normal individual is emphasized.

Bondy, Philip K. (*Dept. of Med., Emory Univ. Sch. of Med., Atlanta, Ga.*): SPONTANEOUS VARIATIONS IN THE RATE OF OUTPUT OF GLUCOSE BY THE LIVER IN NORMAL MAN. Am. J. Med. *13*:642, November 1952 (Abstract of a paper presented at the Sixth Annual Meeting of the Southern Society for Clinical Research, Atlanta, Ga., January 19, 1952).

The rate of output of glucose by the human liver was investigated by estimating the splanchnic glucose balance in normal human beings under basal conditions by the liver catheter technic over periods of time from 5 to 45 minutes at intervals of 30 seconds to 10 minutes. The output was not constant but varied widely and spontaneously to such a degree that in no case was the mean glucose balance significantly different from zero. The use of constant sampling technics failed to alter the situation and introduced additional errors. The author concludes that the estimation of long-term splanchnic glucose balances by the use of the catheter is, therefore, a highly inaccurate and untrustworthy technic. The results reflect only the balance at the moment of sampling.

Bowman, Roger H. (*Dept. of Zool., Cornell Univ., Ithaca, N. Y.*): EFFECT OF COMBINED TREATMENT WITH TESTOSTERONE AND GROWTH HORMONE ON MUSCLE GLYCOGEN IN HYPOPHYSECTOMIZED FEMALE RATS. Am. J. Physiol. *172*:157-61, January 1953.

Testosterone propionate and purified growth hormone were able to maintain glycogen levels above that of the controls in skeletal muscles (rectus femoris, abdominal, diaphragm) of fasted, hypophysectomized female rats (glycostatic effect). Testosterone increased the glycogen level of these muscles in intact female rats as well. When combined injections of testosterone and growth hormone were administered to hypophysectomized female rats, the amount of glycogen deposited could be accounted for by the sum of the effects achieved with hormones when given separately.

A possible seasonal difference in basic glycogen levels was observed in some muscles of fasted, hypophysectomized female rats.

Brousseau, Edward R. (*Omaha, Neb.*): NERVOUS SYSTEM COMPLICATIONS IN DIABETES MELLITUS. Nebraska M. J. 37:352-53, November 1952.

A brief review of the recent literature concerning the neurologic complications of diabetes mellitus has been presented. It has shown that all portions of the nervous systems can be involved. The pathology of such change is usually secondary, and the importance of arteriosclerosis has been emphasized. Personality changes on a neurotic or organic basis are suggested as an important factor in the adequate control of diabetes. In turn, control of diabetes is the best treatment for diabetic neuropathy. The effectiveness of vitamins has been questioned.

Brown, David H.; Park, C. R.; Daughaday, William H.; and Cornblath, Marvin. (*Dept. of Biol. Chem.,*

Washington Univ. Sch. of Med., St. Louis, Mo.): THE INFLUENCE OF PRELIMINARY SOAKING ON GLUCOSE UTILIZATION BY DIAPHRAGM. J. Biol. Chem. *197*:167-74, July 1952.

The authors report that glucose uptake by the rat diaphragm is markedly affected by the conditions under which the tissue is held prior to and during incubation. As much as a two-fold rise was observed as a result of soaking the diaphragm at a low temperature for a period of a few minutes prior to incubation. If the conditions are not carefully controlled, hormonal influences can be obscured. The authors state that when the conditions are adequately controlled, they have never failed to demonstrate qualitatively either the effect of hypophysectomy, of growth hormone, or of insulin.

Colcher, Henry; Drachman, Stanley R.; and Adlersberg, David (*Med. Services, Nutrition Clin. and Div. of Chem., Mount Sinai Hosp., New York, N. Y.*): MANAGEMENT OF INTRACTABLE SPRUE WITH CORTISONE AND ADRENOCORTICOTROPIN (ACTH). Ann. Int. Med. *38*:554-67, March 1953.

Eight patients with the sprue syndrome were treated with 13 courses of cortisone and/or eight courses of ACTH therapy. All but one patient had proved resistant to conventional sprue therapy prior to hormonal administration. The administration of cortisone and ACTH does not represent curative therapy. However, a clinical remission was observed in all cases, the extent varying from patient to patient. Disappearance of the diarrhea, an increased sense of well-being, improvement of appetite and gain of body weight, especially with prolonged treatment, were the important clinical manifestations. In some instances there was improvement of the serum albumin, the serum calcium, the roentgenologic findings in the small intestine and the content of fat in the stools. Multiple courses of treatment with these homones in the same patients resulted each time in clinical improvement of essentially the same degree, in the same interval and on approximately the same dose. No instance of resistance to this form of therapy has thus far developed. One to five weeks after cessation of hormonal therapy, clinical relapses invariably occurred. It was therefore found advisable to maintain therapy-resistant sprue patients on minimal doses of cortisone or ACTH compatible with the regression of their symptoms. The practical management of sprue patients receiving cortisone and ACTH is outlined.

Coleman, Mary C.; Tuttle, W. W.; and Daum, Kate. (*Depts. of Physiology and Nutrition, State Univ. of Iowa, Iowa City, Iowa*): EFFECT OF PROTEIN SOURCE ON MAINTAINING BLOOD SUGAR LEVELS AFTER BREAKFAST. J. Am. Dietet. A. *29*:239-44, March 1953.

Data were collected from 13 normal subjects, 8 males and 5 females, between the ages of sixteen and twenty-seven years relative to the effect of the protein source in breakfast on the course of the blood sugar level following the meal. It was found that the nature of the protein-animal, plant, or a mixture—made no difference.

Cook, Margaret; and Lorber, Victor. (*Dept of Biochemistry, Sch. of Med., Western Reserve Univ., Cleveland, Ohio*): CONVERSION OF 1-C^{14}-MANNOSE AND 1-C^{14}-GLUCOSE TO LIVER AND MUSCLE GLYCOGEN IN THE INTACT RAT. J. Biol. Chem. *199*:1-8, November 1952.

The conversion of mannose to glucose in vivo was studied by use of the isotope distribution patterns found in liver and muscle glycogen after the intraperitoneal administration of 1-C^{14}-mannose[1] and 1-C^{14}-glucose to fasted rats an indicators of the pathways involved. It was concluded that a direct conversion of mannose to glucose, not involving carbon chain cleavage, occurs in mammalian tissue.

[1] 1-C^{14}=1-C^{14}

Cori, Gerty T.; and Cori, Carl F. (*Dept. of Biol. Chem., Washington Univ. Sch. of Med., St. Louis, Mo.*): GLUCOSE-6-PHOSPHATASE OF THE LIVER IN GLYCOGEN STORAGE DISEASE. J. Biol. Chem. *199*:661-67, December 1952.

The glucose-6-phosphatase activity was measured in liver homogenates from 6 cases of von Gierke's disease. In two fatal cases the enzyme was practically absent; this could not be explained by the presence of an inhibitor or by the lack of cofactors. In two out of four surviving cases of von Gierke's disease with mild symptoms, the activity of the specific phosphatase was below the level found in other liver diseases. The pathogenesis of the disease is discussed in terms of a specific enzymatic lesion.

Correspondence—Shepardson, H. Clare (*San Francisco, Calif.*): EFFECT OF ISONIAZID ON DIABETES. Am. Rev. Tuberc. *67*:544, April 1953.

Nydrazid was given to five patients with moderately severe diabetes but without other complications, particularly tuberculosis; 150 mg. daily were prescribed; and the medication was continued for a period of three months. In no instance was the diabetes affected, either favorably or unfavorably. The patients' feelings of well-being were not altered, and no influence was evident on the insulin dosage, the control of the diabetes, or patients' weights. It seems likely that the favorable influence noted on the diabetes in patients with tuberculosis resulted from the effect of the drug on the tuberculosis and not on the diabetes.

Correspondence—Vere, D. W. (*The London Hosp., London, England*): ESTIMATION OF BLOOD-DEXTROSE. *Lancet* 2:1273, Dec. 27, 1952.

The author, in a brief letter, defends the theory behind his recently published method for the rapid estimation of blood sugar with the polarizing ophthalmoscope.

Creery, R. D. G.; and Parkinson, T. J. (*Univ. Dept. of Child Health and the Dept. of Pathology, Southmead Hosp., Bristol, England*): BLOOD GLUCOSE CHANGES IN THE NEWBORN: 1. THE BLOOD GLUCOSE PATTERN OF NORMAL INFANTS IN THE FIRST 12 HOURS OF LIFE. Arch. Dis. Childhood 28:135-39, April 1953.

From a total of 356 estimations, it is concluded that the normal blood glucose range for babies between 1 and 12 hours old is 30 to 75 mg. per 100 ml. There is no difference in blood glucose between male and female babies. There is no relationship between the birth weight of full-term babies and the mean of the blood glucose at 3, 6, 9 and 12 hours.

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de Bodo, R. C.; Sinkoff, M.W.; Kurtz, M.; Lane, N.; and Kiang, S. P. (*Dept. of Pharmacol., New York Univ., Coll. of Med., New York, N. Y.*): SIGNIFICANCE OF ADRENOCORTICAL ATROPHY IN THE CARBOHYDRATE METABOLISM OF HYPOPHYSECTOMIZED DOGS. Am. J. Physiol. 173:11-21, April 1953.

Hypophysectomized dogs manifesting an extreme sensitivity to insulin, an abnormal secondary hypoglycemia during the glucose tolerance test, a slight adrenaline hyperglycemia, and generalized adrenocortical atrophy were given (a) ACTH (corticotropin), (b) adrenal cortical extract, and (c) cortisone or hydrocortisone.

Prolonged administration of potent ACTH preparations either diminished or abolished the insulin hypersensitivity, the secondary hypoglycemia of the glucose tolerance test and the adrenaline resistance. In the majority of the dogs, ACTH produced resistance to insulin (the "test dose") and abnormally high blood sugar rise in response to adrenaline; in some dogs, a tendency towards diabetes also was produced. Four of six dogs had combined adrenal gland weights within the normal range. In all except one dog, histological evidence for adrenocortical hyperplasia was present.

Adrenal cortical extract, in amounts equivalent to 3,750 or 7,500 gm. of adrenal gland given over a period of 18 to 40 hours, only partially abolished the insulin hypersensitivity and produced no appreciable change in the adrenaline response of the hypophysectomized dogs.

Prolonged administration of cortisone or hydrocortisone, in dosages of 0.83 to 1.35 mg. per kg. per day, was sufficient to return to normal the exaggerated response to insulin ("10 times the test dose"—0.25 units per kg. intravenously) and the abnormal glucose tolerance of adrenalectomized dogs. Similar dosage regimens only diminished, but never abolished, the exaggerated response to 10 times the test dose of insulin of all the hypophysectomized dogs. At the same time, the response to the "test dose" of insulin (0.025 unit per kg. intravenously), the secondary hypoglycemia of the glucose tolerance test and the adrenaline resistance were either diminished or abolished.

The effects of adrenocortical steroids upon carbohydrate metabolism seen in the adrenal cortical extract and cortisone and hydrocortisone experiments are of a long-lasting nature.

It is concluded that: (a) the adrenocortical atrophy is but one factor responsible for the abnormalities in carbohydrate metabolism of hypophysectomized dogs; (b) in addition, absence of anterior pituitary hormone(s) other than ACTH contributes to the production of those abnormalities; (c) the anterior pituitary hormone(s), therefore, participates in the endocrine control of normal carbohydrate metabolism; and (d) the long-lasting action of administered adrenocortical steroids is due, possibly, to some secondary metabolic adjustment rather than to the actual presence of these hormones in the organism.

Dewind, L. T.; Michaels, G. D.; and Kinsell, L. W. (*Inst. for Metabolic Res., Highland Alameda County Hosp., Oakland, Calif.*): LIPID STUDIES IN PATIENTS

WITH ADVANCED ATHEROSCLEROSIS. Am. J. Med. *13*: 499-500, October 1952 (Abstract of paper presented at the Western Sectional Meeting of the American Federation for Clinical Research in Carmel, Calif., January 24, 1952).

A group of 24 diabetic patients with advanced atherosclerosis, many of them having lost extremeties as the result of atherosclerotic involvement, were studied. No significant changes in the diabetic state or in blood lipids were observed in patients receiving relatively large amounts of inositol or choline. Depression of serum cholesterol esters, serum phospholipids, and serum lipoprotein was observed in most patients receiving testosterone propionate in a dose of 25 mg. daily. Some changes in insulin requirement were also noted. These changes were not constant. Serum total cholesterol, lipoprotein, cholesterol ester and phospholipid values varied over a wide range. No obvious correlation between any of the lipid fractions and the atherosclerotic process was found. Linear mathematical correlation was noted between the lipoprotein and total cholesterol, lipoprotein and cholesterol esters, cholesterol esters and serum phospholipids. The authors conclude that (1) testosterone propionate appeared to have some effect upon certain lipid constituents of the blood and (2) that there was no obvious correlation between *any* of the lipid components studied and the atherosclerotic process.

Dolger, Henry (*Diabetes Clin. of Mount Sinai Hosp., New York, N.Y.*): DENATURED INSULIN: A SIMPLIFIED, RAPID MEANS OF TREATMENT OF ALLERGY TO INSULIN COMPLICATING DIABETIC KETOSIS. New York State J. Med. 52:2023-24, August 15, 1952.

Four patients with constitutional allergic reactions and six patients with fairly severe local cutaneous reactions were treated with uniform success by insulin "denatured" by immersion of the vial of insulin in boiling water for 30 minutes. Only the clear, rapidly acting, unmodified insulins, regular or crystalline zinc, can be used in this way.

Dratz, Arthur F.; and Handler, Philip (*Dept. of Biochemistry and Nutrition, Duke Univ. Sch. of Med., Durham, N. C.*): RENAL PHOSPHATE AND CARBOHYDRATE METABOLISM STUDIED WITH THE AID OF RADIOPHOSPHOROUS. J. Biol. Chem. *197*:419-31, July 1952.

The paper presents the results of a study in which radioactive phosphorous was employed in an investigation of renal carbohydrate and phosphate metabolism. The time-course of the specific activities of various phosphate esters in the kidneys of normal, phlorizinized and glucose-treated cats was determined. The difficulties in attempting to demonstrate the mechanism of tubular transport of glucose or phosphate by this technic are discussed in the light of the metabolic and histologic heterogenicity of the kidney.

Dury, Abraham (*Dorn Lab. for Med. Res., Bradford Hosp., Bradford, Pa.*): ADRENAL WEIGHT AND ASCORBIC ACID CONCENTRATION IN ALLOXAN-INJECTED RATS. Proc. Soc. Exper. Biol. & Med. *82*:92-95, January 1953.

The mean adrenal weight per 100 gm. body weight and the adrenal ascorbic acid concentration of groups of rats approximately 3 days after subcutaneous or intravenous injection of alloxan were shown to be significantly greater than the respective mean values in intact rats. The extent of adrenal ascorbic acid depletion 60 minutes after subjection to an acutely stressful condition (208 mg. glucose solution administered intravenously) in intact and alloxan-injected groups was practically identical; and significantly lower concentration than control values were obtained. The results were discussed in relation to whether adrenal ascorbic acid concentration may be considered a reliable guide of hyper or hypofunction of the adrenal cortex.

Editorial (*New York, N. Y.*): DIABETES WEEK. New York State J. Med. *52*:2739, November 15, 1952.

The objectives and values of Diabetes Week are discussed.

Editorial (*New York, N. Y.*): PROTEIN METABOLISM IN DIABETES. Nutrition Rev. *2*:15-17, January 1953.

One of the chief symptoms of severe untreated diabetes is generalized wasting of the body, an indication that proteins as well as fats are sacrificed. Whether this protein loss is a direct consequence of the lack of insulin or is due to secondary effects of the diabetes, such as ketosis, malnutrition or renal failure, has long been a controversial question among clinicians. By making the assumptions that amino acids and proteins constitute two separate homogeneous pools of nitrogen and

that the rate at which nitrogen moves out of either pool is proportional to its concentration in that pool, one could calculate the average rate of synthesis of proteins from amino acids and the average rate of amino acid catabolism. By this method—the theoretic foundation of which is admittedly open to criticism—Hoberman was able to conclude that in alloxan-diabetes there is both depression of protein synthesis from amino acids and acceleration of protein breakdown.

It appears probable that the main effect of diabetes on protein metabolism is to decrease the rate of muscle protein synthesis. This tissue contains the bulk of body protein, and the decrease in formation rate of the order of 60 to 80 per cent, observed by Forker and his collaborators in diabetic animals, is sufficient to account for the loss of body protein in diabetes. While much remains to be explained concerning the mechanism of this decrease in protein synthesis, the reports of Hoberman, and especially those of Chaikoff and his co-workers, represent essential contributions to our understanding of metabolism in diabetes.

Editorial (*London, England*): A NEW LONG-ACTING INSULIN. British Medical Journal *1*:266, January 31, 1953.

Since only one injection a day of this new insulin is needed, it is certainly worthy of further trial; and if it produces more constant results than mixtures of protamine zinc insulin and soluble insulin, it will be much appreciated. A minor drawback is the introduction of one and perhaps three more insulins to those already available. Doctors who seldom have to treat diabetes, and patients new to insulin, are occasionally confused by the varieties in use at present. However, if the new insulins give a better control of the disease, this is a difficulty which must be faced and which experience will soon eradicate.

Elrick, Harold (*Res. Inst., Montreal Genl. Hosp., Montreal, Canada*): PANCREATIC HYPERGLYCEMIC FACTOR AND GROWTH. Proc. Soc. Exper. Biol. & Med. *82*:76-79, January 1953.

Purified preparations of pancreatic hyperglycemic factor have been shown to increase the width of the epiphyseal cartilage of the hypophysectomized rat when assayed by the tibia test used for the bioassay of pituitary growth hormone. The activity of the preparations found by this assay parallels their glycogenolytic activity in vitro.

Engel, Frank L.; and Burns, Thomas W. (*Dept. of Med., Duke Univ. Sch. of Med., Durham, N. C.*): STUDIES ON THE METABOLIC RESPONSE TO INJURY: ROLE OF THE ADRENAL CORTEX IN CARBOHYDRATE METABOLISM DURING ILLNESS. Am. J. Med. *13*:643, November 1952 (Abstract of a paper presented at the Sixth Annual Meeting of the Southern Society for Clinical Research, Atlanta, Ga., January 19, 1952).

In a series of 200 glucose, glucose-insulin and insulin tolerance tests on 87 normal and 40 ill subjects untreated but receiving 200 to 400 mg. of oral cortisone four hours before testing or 200 mg. daily for seven days, it was found that (1) the response of normal subjects to these tests was in general significantly different from those of ill individuals; (2) the response of normal subjects given cortisone was significantly different from ill subjects and (3) ill subjects receiving cortisone exhibited strikingly greater impairment in carbohydrate tolerance than did normal subjects similarly treated with cortisone. The authors maintain that these results support the concept, based on extensive studies with animals in their laboratory, that adrenal hormone in amounts beyond that necessary to sustain response to injury sensitizes the organism to overrespond to damage.

Essellier, A. F.; Jeanneret, R. L.; and Koszewski, B. J. (*Medizinischen Universitätsklinik Zürich*): NPH INSULIN, A NEW INTERMEDIARY INSULIN: COMPARATIVE CLINICAL INVESTIGATIONS. Schweizerische medizinische Wochenschrift *82*:549, 1952.

The authors believe that NPH insulin is the preparation of choice for the treatment of moderately severe and severe cases of diabetes mellitus.

Evans, Cyril; and Stradling, Peter (*London, England*): EFFECT OF ISONIAZID ON CARBOHYDRATE METABOLISM: CASE REPORT. British Medical Journal *1*:729-30, March 28, 1953.

A patient apparently developed diabetes mellitus during a course of isoniazid therapy for pulmonary tuberculosis. Cause and effect have not been proved, however, and the case is presented without comment.

Fabrykant, Maximilian (*Dept. of Med., N. Y. Univ. Post-Grad. Med. Sch. and Univ. Hosp., New York, N. Y.*): FURTHER STUDIES ON ELECTROCEREBRAL DYSFUNCTION AND THE USE OF ANTI-CONVULSANTS IN LABILE DIABETES. Ann. Int. Med. *38*:814-23, April 1953.

In a group of 15 labile diabetics, electroencephalographic abnormalities were recorded in 80 per cent and severely disordered patterns consistent with convulsive tendency or focal pathology in almost 50 per cent of the patients. A genetic factor responsible for the abnormal brain potentials was present in three patients, while in one patient a typical epilepsy was considered as a causative factor. The distorted patterns in the remaining patients were attributed to disturbed brain function resulting from repeated severe insulin reactions. It was shown that the abnormal electrocerebral activity reduced the threshold for insulin reactions, increased their intensity and lowered their responsiveness to carbohydrate therapy. It also produced pseudohypoglycemic reactions occurring in absence of critical hypoglycemia. The effectiveness of anticonvulsive drugs in the management of labile diabetes associated with electrocerebral dysfunction was confirmed, and it was concluded that abnormal brain waves in labile diabetes do not always represent irreversible injury to the brain. It was also concluded that abnormal brain potentials are not the only cause or the prerequisite of lability in diabetes.

Fajans, Stefan S. (*Dept. of Internal Med., Univ. of Michigan, Ann Arbor, Mich.*): RECENT ADVANCES IN THE MANAGEMENT OF DIABETIC COMA. Nebraska M. J. 37:347-52, November 1952.

The major part of this discussion deals with potassium therapy, considered the oustanding contribution to the treatment of diabetic coma within the last few years.

Flock, Eunice V.; Block, Melvin A.; Mann, Frank C.; Grindlay, John H.; and Bollman, Jesse L. (*Div. of Experimental Med., Mayo Foundation, Univ. of Minnesota, Rochester, Minn.*): THE EFFECT OF GLUCOSE ON THE AMINO ACIDS OF PLASMA AFTER TOTAL HEPATECTOMY. J. Biol. Chem. *198*:427-37, September 1952.

The individual amino acids were observed to increase together in the plasma of hepatectomized dogs not receiving glucose or maintained with minimal amounts of glucose. Administration of large amounts of glucose was found to minimize the increase of amino acids of the plasma and produced a decrease in the amount of accumulated amino acids. These observations suggested to the authors that glucose or insulin exert a nitrogen-sparing action by increasing the rate of amino acid incorporation in the tissues.

The effect of nephrectomy was also investigated. Normal values were found after bilateral nephrectomy in the dogs, and the increase following total hepatectomy was similar, whether or not bilateral nephrectomy was also performed. The increase of amino acid nitrogen in the blood of dehepatized, nephrectomized dogs was found to be less than the increase of urea which occurs in nephrectomized dogs.

About the same proportion of the total dialyzable amino acid nitrogen of both plasma and urine was present in a combined form before and after hepatectomy.

Galley, A. H. (*Surrey, England*): CAUDAL ANALGESIA —CLINICAL APPLICATIONS IN VASOSPASTIC DISEASES OF THE LEGS AND IN DIABETIC NEUROPATHY. Proceedings of the Royal Society of Medicine *45*:748-52, November 1952 (Abstract from J.A.M.A. *151*:954-55, March 14, 1953).

The author describes clinical experiences with caudal analgesia in patients with cold feet, vasospastic disease of the legs, phlegmasia alba dolens and diabetic neuropathy. Caudal analgesia supplies a form of multiple paravertebral block that necessitates only one injection. The injection of intermittent doses of aqueous analgesic solutions or single injections of oily solutions often break the cycles of pathological events associated with vasospastic disease of the leg or diabetic neuropathy.

Given, William P. (*Dept. of Obst. and Gynec., New York Hosp., New York, N. Y.*): DIABETES COMPLICATING PREGNANCY. New York State J. Med. *52*:2794-98, November 15, 1952.

Management of diabetes complicating pregnancy is discussed, with special emphasis on prevention of complications, early delivery by the method which sound obstetric judgment indicates at the time and expert pediatric care.

Gottfried, Sidney P.; Natelson, Samuel; and Pincus, Joseph B. (*Biochemical Res. Unit, Veterans Adminis-*

tration Hosp., Northport, N. Y.; Pediat. Res. Lab. of the Jewish Hosp. of Brooklyn, Brooklyn, N. Y.): RESPONSE OF SERUM CITRIC ACID LEVELS IN SCHIZOPHRENICS TO THE INTRAMUSCULAR ADMINISTRATION OF INSULIN. J. Nerv. & Ment. Dis. *117*:59-64, January 1953.

Serial serum glucose and citric acid tests were performed on 12 adult male schizophrenics after the intramuscular administration of 20 units of insulin. Seven of the 12 cases showed an abnormal response to insulin. The hypothesis is advanced that this abnormal response was due to an excessive secretion of epinephrine which neutralized the action of the administered insulin. Serum calcium, glucose and citric acid tests were performed on 26 adult male schizophrenics before and after the administration of 80 to 300 units of insulin. Twenty of the 26 cases showed a lowering in the serum citric acid, and the other 6 cases showed either no change or a rise in the serum citric acid. Here, too, the hypothesis is advanced that the results obtained in the above 6 cases were due to an excessive secretion of epinephrine.

Guggenheim, K.; and Mayer, J. (*Dept. of Nutrition, Harvard Med. Sch. of Pub. Health, Boston, Mass.*): STUDIES OF PYRUVATE AND ACETATE METABOLISM IN THE HEREDITARY OBESITY-DIABETES SYNDROME OF MICE. J. Biol. Chem. *198*:259-65, September 1952.

Studies of pyruvate and acetate metabolism in the hereditary obesity-diabetes syndrome of mice were conducted. When fasted obese and nonobese mice were injected with carboxyl-labeled sodium acetate, the nonobese mice excreted significantly (one-third) more labeled CO_2 during the 3 hours following injection than did the obese animals. When obese and nonobese animals were fed labeled acetate for 3 days, over-all incorporation of labeled carbon was more than twice as great in the obese as in the nonobese. By means of carboxyl-labeled pyruvate, it was shown that pyruvate oxidation was also depressed in the obese animals, although to a lesser extent than in alloxan-diabetic nonobese mice. The partial block of acetate utilization and resultant increased lipogenesis are considered by the authors to represent the primary hereditary biochemical lesion in the syndrome.

Gutmann, M. J. (*Jerusalem, Israel*): ANTAGONISM BETWEEN DIABETES MELLITUS AND ALLERGIC DISEASES, ESPECIALLY BRONCHIAL ASTHMA. International Archives of Allergy and Applied Immunology *4*:118-28, 1953.

The incidence of diabetes in the families of allergic patients remains lower than in the general population. On the other hand, we find an augmented number of diabetics in the families of individual allergic patients. Examples and family histories are given. Of 12 asthmatics treated with Cortone or ACTH, four showed a high glycosuria and hyperglycemia that made reduction of the doses or interruption of this treatment necessary. These four patients showed cases of diabetes in their families; the remaining eight had no such history.

Hallas-Moller, K.; Jersild, M.; Petersen, K.; and Schlichtkrull, J. (*Hvidore Hosp., Copenhagen, Denmark*): ZINC INSULIN PREPARATIONS FOR SINGLE DAILY INJECTION: CLINICAL STUDIES OF NEW PREPARATIONS WITH PROLONGED ACTION. J. A. M. A. *150*:1667-71, December 27, 1952.

Preparations of the zinc insulin type can be made with considerably varied ranges of activity. These preparations are mutually miscible and, because of this, the range of activity can be further varied.

Investigations have been concentrated on three types of zinc insulin preparations: (a) a suspension of amorphous precipitated insulin, containing 2 mg. of zinc per 1,000 units, with a *p*H of 7.2 and an average activity range of about 18 hours; (b) a suspension of ground insulin crystals (particle size about 0.002 mm.), containing 2 mg. of zinc per 1,000 units of insulin, with a *p*H of 7.2 and an average activity range of about 24 hours and (c) a suspension of insulin crystals (particle size 0.01 to 0.02 mm.) containing 2 mg. of zinc per 1,000 units of insulin, with a *p*H of 7.2 and an average activity range of about 30 hours.

Satisfactory blood sugar control can be obtained with a single daily injection of the appropriate one of the three types of zinc insulin. Such a series of insulin preparations provide a simplified technic for the adjustment of patients with severe cases of diabetes. It is possible that only two types of zinc insulin preparations may be necessary because of the miscibility of such preparations.

Hartford, John J. (*Cincinnati Gen. Hosp., Cincinnati, Ohio*): RETINAL VASCULAR CHANGES IN DIABETES MELLITUS. Am. J. Ophth. *36*:324-30, March 1953.

Diabetes mellitus of itself, without hypertension or arteriosclerosis, produces deleterious effects upon the retinal vasculature. The changes are predominantly in the capillary tree and are more numerous toward the venous side.

Microaneurysms, although not pathognomonic of diabetes mellitus, are found much more frequently and in greater numbers in the retinas of patients with long-standing cases of this disease and occur in any quadrant of the fundus. Some appear to be the sites of hemorrhages.

Perseverance in maintaining day-to-day optimum conditions for the patient with diabetes mellitus is noted by some investigators to minimize the deleterious effects that the long duration of this disease has upon vision.

Haugaard, Ella S.; and Stadie, William C. (*John Herr Musser Dept. of Res. Med., Univ. of Pennsylvania, Philadelphia, Pa.*): RELATION BETWEEN GLYCOGEN CONTENT AND SYNTHESIS OF FATTY ACIDS BY RAT LIVER. J. Biol. Chem. *199*:741-44, December 1952.

The glycogen content of rat livers was altered over a wide range by varying the antecedent diet. The rate of incorporation of C^{14} acetate into fatty acids by slices of such livers was determined. A significant positive correlation was found between the initial concentration of glycogen and the ability of the slices to synthesize fatty acids from acetate.

Henson, Waldo C.; and Heffner, George P. (*Charleston, W. Va.*): WEST VIRGINIA'S CAMP FOR JUVENILE DIABETICS (A Follow-Up Report on Camp Kno-Koma). West Virginia M. J. *49*:127-29, May 1953.

By carefully controlling the diet and insulin, the juvenile diabetic can live a perfectly normal recreational and social life. Inconstant glycosuria and often acetonuria may be insignificant. Between-meal snacks and bedtime feedings often are necessary and are included as part of the total diet. Insofar as camp life is concerned, single morning insulin injections are usually effective.

One of the greatest services the camp has rendered is enabling children, who often are inhibited and withdrawn, to expand and develop greater interests and confidence in themselves in facing future problems of life.

Hirson, Cedric. (*West Herts Hosp., Hemel Hempstead, Herts, England*): LOCALIZED MUSCULAR ATROPHY IN DIABETES. Lancet *1*:968-69, May 16, 1953.

Six cases are reported in which there were localized areas of muscular atrophy, suggesting that a specific process independent of insulin atrophy was operating. In the present cases, the usual sites of injection have been spared, and the characteristic induration found with insulin lesions has been absent. The atrophy has been found in unusual places for injection. Half the cases described showed neurological abnormalities, but the muscle lesions did not correspond to any nerve distribution.

Holmes, Joseph H.; and Montgomery, A. V. (*Dept. of Med. & Physiol., Univ. of Colorado Sch. of Med., Denver, Colo.*): THIRST AS A SYMPTOM. Am. J. M. Sc. *225*:281-86, March 1953.

The authors review clinical situations in which thirst may be important to diagnosis or therapy. These are dehydration, cardiac edema, polyurias of endocrine origin, hemorrhage leading to shock and diseases altering salivary secretion, such as myasthenia gravis and emotional disturbances. The physiologic mechanisms involved in thirst are not clearly understood but appear to be related to the rate of salivary flow and/or to intracellular dehydration and are influenced by reflexes arising from the stomach. Observation of the rate of salivary secretion constitutes one method of differentiating between true thirst and excessive water drinking; it is increased by pitressin administration in the former instance and is decreased or unaffected in the latter.

Hotta, S.; and Chaikoff, I. L. (*Div. of Physiol. of the Univ. of California Sch. of Med., Berkeley, Calif.*): CHOLESTEROL SYNTHESIS FROM ACETATE IN THE DIABETIC LIVER. J. Biol. Chem. *198*:895-99, October 1952.

An increased incorporation of acetate carbon into cholesterol by liver slices from alloxan-diabetic rats was demonstrated. It was further shown that, as a result of insulin injections in a diabetic rat, slices subsequently prepared from its liver have a reduced capacity to synthesize cholesterol. The ratio of incorporation of methyl to carboxyl carbons of acetate into cholesterol by the diabetic liver was the same as that observed with normal livers.

Illingworth, Barbara; Larner, Joseph; and Cori, Gerty T. (*Dept. of Biol. Chem., Washington Univ. Sch. of Med., St. Louis, Mo.*): STRUCTURE OF GLYCOGENS AND

AMYLOPECTINS. I. ENZYMATIC DETERMINATION OF CHAIN LENGTH. J. Biol. Chem. *199*:631-40, December 1952.

A partial determination of structure was carried out on glycogens isolated from livers of different animal species as well as from the livers of the same species under different conditions. This consisted of the determination of the degree of branching and of the average number of glucose residues in the outer and inner branches. The degree of branching decreased in glycogens isolated from the livers of embryonal, newborn and young adult guinea pigs. A similar decrease was also noted in phytoglycogen isolated from immature, mature and overmature sweet corn.

Illingworth, Barbara; and Cori, Gerty T. (*Dept. of Biol. Chem., Washington Univ. Sch. of Med., St. Louis, Mo.*): STRUCTURE OF GLYCOGENS AND AMYLOPECTINS. III. NORMAL AND ABNORMAL HUMAN GLYCOGEN. J. Biol. Chem. *199*:653-60, December 1952.

Glycogen was isolated from the livers of 10 children with von Gierke's disease. Structure analysis consisted of the determination of the degree of branching and of the length of outer and inner chains. In two cases, an analysis was carried out by stepwise enzymatic degradation. Human liver and muscle glycogen from control cases were similarly analyzed in order to establish the extent of individual variation. In 8 out of the 10 cases no abnormality of glycogen structure could be detected. In one case of storage disease involving both liver and skeletal muscle, the liver glycogen had very short outer branches and the muscle glycogen had almost none. In another case, the liver glycogen was less branched and had longer inner and outer chains than normal glycogen. A deficiency of the specific glucose-6-phosphatase of the liver was demonstrated in the two fatal cases in which glycogen structure was normal. According to the authors, the two cases with abnormal glycogen structure point to different kinds of enzymatic deficiency and emphasize the fact that there are different types of glycogen storage disease.

Ingle, Dwight J. (*Res. Lab., The Upjohn Co., Kalamazoo, Mich.*): EFFECTS OF ADMINISTERING CORTISONE ACETATE AND DIETHYLSTILBESTROL TO NORMAL FORCE-FED RATS. Am. J. Physiol. *172*:115-18, January 1953.

Normal rats were force-fed a medium carbohydrate diet by stomach tube. Cortisone and diethylstilbestrol were administered separately and in combination for 14 days. A dose of 1 mg./rat/day of diethylstilbestrol failed to cause glycosuria or loss of weight in any of the rats; but when it was given in addition to cortisone (doses of 0.5, 1, 2 and 5 mg./rat/day), the response to the latter compound, as evidenced by glycosuria and loss of weight, was greatly enhanced.

Joyner, Claude R., Jr. (*Med. Serv., U. S. N. Hosp., Oakland, Calif.*): ESSENTIAL HYPERLIPEMIA. Ann. Int. Med. *38*:759-77, April 1953.

The clinical and laboratory features of essential or "idiopathic" hyperlipemia have been presented and another case report added to the literature. It is a disease which is diagnosed largely by exclusion and which responds well to simple dietary fat restriction. It is seen that varied manifestations of this condition make it an important, although rare, disease. The history and laboratory findings of a case of essential hyperlipemia have been reported. The beneficial effect of dietary fat restriction on the lipid values and symptomatology was prominent. Tests for endocrine, metabolic, renal, hepatic and gastrointestinal abnormalities have been summarized and discussed. The prognosis in the disease was considered, and an attempt was made to determine the likelihood of premature atherosclerosis in such a patient. The author's studies and present-day evidence would indicate that a patient with essential hyperlipemia is more likely to develop atherosclerosis than his counterpart with normal fat absorption, deposition and utilization. The long-term study of this type of patient might well prove informative in the investigation of the genesis of atherosclerosis.

Kaechele, E.; and Petrides, P. (*Düsseldorf Academy of Medicine, Germany*): CLINICAL EXPERIENCES WITH DI-INSULIN-NOVO. Münchener medizinische Wchnschr. *17*:491-92, April 1953.

The action of Di-insulin with its two action maxima is capable of treating alimentary hyperglycemias. The decreased latitude of fluctuation of the daily blood sugar curve means at the same time a stabilization of the metabolic condition in general. The domain of Di-insulin as a combination insulin with relatively brief protraction of the depot components lies with diabetics with a larger insulin requirement who need 2 injections daily. The application of Di-insulin to patients who are well ad-

justed with a larger dose of an insulin with more prolonged action in one single injection does not seem generally to bring any improvement in the metabolism because the depot portion in Di-insulin is not then sufficient.

Karvinen, E.; and Karvinen, M. J. (*Physiol. Inst., Univ. of Helsinki, and the Inst. of Occupational Health, Helsinki, Finland*): THE EFFECT OF INSULIN HYPOGLYCAEMIA ON HISTAMINE-INDUCED HEIDENHAIN POUCH SECRETION IN THE DOG. Acta physiologica Scandinavica 27:350-70, February 1953.

The volume, *p*H, titratable acidity, free HCL and the total chlorides of Heidenhain pouch secretion induced by histaminè has been observed in three dogs during insulin hypoglycemia. Body temperature was recorded. Experiments in which the production of hypoglycemia after insulin was prevented by an injection or infusion of glucose were also performed. It was concluded that insulin hypoglycemia has an inhibiting effect on canine gastric secretion of acid induced by histamine. This inhibition is mainly due to hypoglcemia.

Keerberghen, J. Van; and Lederer, J. (*Brussels, Belgium*): PAPILLARY NECROSIS WITH CHRONIC EVOLUTION IN THE DIABETIC. La Presse Médicale 60:1745-47, December 25, 1952.

Two cases of papillary necrosis with chronic evolution occurring in diabetics are described. Diagnosis was made on the bases of the occurrence, on one hand, of characteristic radiologic pictures and, on the other hand, of hemorrhages of renal origin of very capricious nature with moderate pyuria.

Kempe, C. H.; Silver, H. K.; Carr, J.; Smyth, F. S.; Gofman, J. W.; and Jones, H. B. (*Div of Ped., Univ. of California Sch. of Med., San Francisco, Calif., and the Donner Lab., Div. of Med. Physics and Radiation Lab., Univ. of California, Berkeley, Calif.*): LIPOPROTEINS OF SERUM IN NORMAL AND DIABETIC CHILDREN. Am. J. Med. 13:500, October 1952 (Abstract of paper presented at the Western Sectional Meeting of the American Federation for Clinical Research in Carmel, Calif., January 24, 1952).

Measurements of the concentration of S_f 11-20 lipoprotein molecules were made in the serums of 147 normal children ranging in age from birth to 15 years, in the serums of 12 women and their newborn infants, and in the serums of 46 juvenile diabetics. Values in the normal male children were similar to those obtained from normal female children and approximated those of normal female adults between the ages of 21 and 30 years. They were significantly lower than those of normal male adults of this age group. Newborn infants had lower levels of this class of molecules than their own mothers in each instance. Levels were found to be unrelated to the daily intake of fat per unit of body weight in the pediatric age group. No correlation with analytical serum cholesterol was found.

Values obtained for diabetic girls were higher than those for diabetic boys. These diabetic boys, however, had serum levels of the S_f 11-20 molecules higher than their normal counterparts. No correlation was found between these levels and the duration and severity of the diabetic state, dietary intake of fat or the serum cholesterol levels.

Kibler, Robert F.; Taylor, W. Jape; and Myers, J. D. (*Dept. of Med., Duke Univ. Sch. of Med., Durham, N. C.*): EFFECTS IN MAN OF THE HYPERGLYCEMIC-GLYCOGENOLYTIC FACTOR OF THE PANCREAS. Am. J. Med. 13:647, November 1952 (Abstract of a paper presented at the Sixth Annual Meeting of the Southern Society for Clinical Research, Atlanta, Ga., January 19, 1952).

Employing the technic of hepatic venous catheterization, the authors found that hyperglycemic-glycogenolytic factor (HGF), 5 mg. intravenously, caused a mean rise in arterial blood glucose of 22 mg. per 100 cc. within ten minutes. Hepatic venous glucose concentration rose more abruptly and more intensely to a mean of +36 mg. within five minutes. Splanchnic glucose production increased at the peak of 250 per cent of the control value. These results in the control group of subjects were very consistent.

Preliminary studies in Laennec's cirrhosis, hyperthyroidism and states of malnutrition (conditions in which hepatic glycogen would be expected to be reduced) showed a subnormal response to HGF as judged by augmentation of arterial blood glucose concentration. Two patients with myxedema gave normal responses.

The authors conclude that HGF causes hyperglycemia in man by strikingly increasing splanchnic, presumably hepatic, glucose production and that the response to the material may prove to be a measure of hepatic glycogen content.

Kimmelsteil, Paul (Charlotte, No. Carolina): FUNCTION AND MORPHOLOGY IN THE CLASSIFICATION OF NEPHROSES. South. M. J. *46*:175-81, February 1953.

The author presents a classification of the nephroses, subdivided into (a) glomerular, (b) tubular and (c) vascular, based upon an integration of morphology and function.

Kinsell, Laurance W.; Michaels, George D.; Margen, Sheldon; Boling, Lenore; and Partridge, John W., with technical assistance of Dawson, Nancy; Fukayama, George; Greer, Rosalie; and Smyrl, Sadie (*Inst. for Metabolic Res., Highland Alameda County Hosp., Oakland, Calif.*): ACCELERATION OF NEOGLUCOGENESIS FROM FAT IN RESPONSE TO ACTH AND CORTISONE IN HUMAN SUBJECTS. Am. J. Med. *13*:96-97, July 1952. (Abstract of paper presented at the Fifth Annual Meeting of the Western Society for Clinical Research, Carmel, Calif., January 25 and 26, 1952).

The experimental work was designed to determine the presence or absence of acceleration of neoglucogenesis from fatty acids by ACTH and cortisone. Three diabetic subjects were maintained on chemically constant formula intake throughout the twenty-four hours. The formulas contained no carbohydrate, large amounts of fat, and different amounts of protein in each of the three subjects. After a suitable control period all patients received ACTH and/or cortisone.

The following results were obtained: (1) Major increase in glycosuria and urinary nitrogen occurred in all instances during ACTH and cortisone administration. (2) The proportional increase in urinary sugar was significantly greater than the increase in urinary nitrogen. In numerous instances during the course of each of the three studies the D/N ratio greatly exceeded 3.65. At times, the ratio actually exceeded 6.25. (3) In two of the patients, major insulin resistance resulted from the administration of ACTH and cortisone. In the third patient (in whom the experimental procedures were modified), no insulin resistance occurred despite progressive hyperglycemia and glycosuria. The authors conclude from these findings that cortisone-like steroids resulting from adrenocortical stimulation accelerate the formation of carbohydrate from fatty acid.

Klinger, R.; and Dalle Coste, P.: COCARBOXYLASE IN TREATMENT OF DIABETIC ACIDOSIS AND SOME DIABETIC COMPLICATIONS. Minerva medica *43*:1158, November 26, 1952. (Abstract from J.A.M.A. *151*:1455, April 18, 1953).

Cocarboxylase ("bioxilase") was used intramuscularly to treat 62 patients with diabetes in whom complications had developed. The dose, proportional to the severity of the complication, ranged from 25 mg. to 100 mg. daily for 3 to 50 days. Results were gratifying in 83.3 per cent of the patients. In one patient treatment had to be interrupted because pain and paresthesia developed in the extremity where the drug had been injected.

Knick, B.; and Wehr, J. (*Univ. Clin., Mainz*): ACTION OF INSULIN IN APPLICATION CLOSE TO THE ORGANS THROUGH AEROSOL. Klinische Wochenschrift *31*:310-11, April 1, 1953.

Fleeting hypoglycemic effects with only mild preliminary stages of clinical hypoglycemia syndromes have been observed after aerosol administration of insulin in the upper respiratory tract. There was quantitative limitation of insulin action with ineffectiveness of large dosage increases, in spite of facilitation by hyaluronidase.

Kodousek, R.; and Endrys J.: DIABETES MELLITUS. Casapis lekaru ceskyck *91*:10-15, 1952. (Abstracted from Excerpta Medica 7:446-47, March 1953).

Using a modification of Bodian's method, the authors studied the histology of the islets of Langerhans in diabetics and in normal subjects. They confirmed the statement of Ferner that in diabetics the number of argentophil cells in the islets is larger than that of the anargentophil cells. The ratio of anargentophil cells to argentophil cells was established in diabetics and in nondiabetics. When this ration (average insular index) is less than 1.1, a histological diagnosis of diabetes is justified. In normal subjects, the ratio is 2 or more.

Koster, Rudolf (*Dept. of Pharmacol., Tulane Univ., New Orleans, La.*): ACUTE EFFECTS OF ORAL GLUCONATES IN DIABETES. Federation Proc. *10*:315-16, March 1951.

Oral sodium gluconate reduced ketones in 13 young adult diabetic Carworth rats. Thirteen days after alloxan, gluconate solutions replaced water for 3 to 6 days, each. Concentration proved more significant than dose; effects were delayed. The reaction of the urine rose from below *p*H 6 to *p*H 9 on the second day after doses of 8 per cent (2 gm. per kg.) or 10 per cent (8 gm. per kg.) sodium gluconate despite subnormal intake of

fluid, whereas much larger doses at lower concentrations, respectively, were ineffective. Alkalinity persisted one day after withdrawal. Ketones disappeared after 3 gm. per kg. of 8 per cent sodium salt, 3 gm. per kg. of 5 per cent potassium salt, 1 gm. per kg. of 5 per cent acid, or 5 gm. per kg. of 4 per cent acid. Sugar in the urine was unchanged by up to 30 gm. per kg. of 7 per cent sodium gluconate but disappeared on the second day after 10 to 30 gm. per kg. of 8 per cent and sometimes after 3 to 10 gm. per kg. of 5 per cent potassium salt. Sugar reappeared one day after drug withdrawal.

Kydd, David M.; Heinsen, A. J.; Hald, Pauline M.; and Peters, John P. (*Dept. of Int. Med., Yale Univ. Sch. of Med., New Haven, Conn.*): GLYCOLYSIS OF BLOOD IN DIABETIC ACIDOSIS. J. Appl. Physiol. 5:647-57, May 1953.

In severe diabetic acidosis, the organic acid soluble phosphate of the blood cells became depleted. This depletion appears to arise from impairment of the process of glycolysis in the blood.

Larner, Joseph; Illingworth, Barbara; and Cori, Gerty T. (*Dept. of Biol. Chem., Washington Univ. Sch. of Med., St. Louis, Mo.*): STRUCTURE OF GLYCOGENS AND AMYLOPECTINS. II. ANALYSIS BY STEPWISE ENZYMATIC DEGRADATION. J. Biol. Chem. *199*:641-51, December 1952.

Four branched polysaccharides (derived from rabbit muscle and liver glycogen, corn and wheat amylopectin) were degraded 80 to 90 per cent by separate and successive action of phosphorylase and amylo-1, 6-glucosidase. The values found after each enzymatic step could be made to fit only one model, namely, the one representing the four polysaccharides as multibranched, tree-like structures.

Lawrence, R. D. (*King's Coll. Hosp., London, England*): DIABETES. Med. Illus. 7:323-24, May 1953.

In social advances Britain has led the world in several ways. It was the first country to form a Diabetic Association, unique in being composed primarily of a body of lay diabetics to look after their own social interests and to further and to support research. From its start in 1933, it has been closely linked with interested doctors, a happy combination of efforts. The Council of the Association is two-thirds laymen, but any clashing interests—which have rarely arisen—have happily been blessed by the spirit of sane compromise.

In social matters, many prejudices of pre-insulin days in relation to employment and life insurance have been fought with increasing success. More important, diabetic convalescent homes have been established for both men and women; not only is proper food and insulin provided, but also the patient is further trained in the diabetic life before going home to ordinary duties and work. Diabetic children have been a very important aspect of the work. Most grow up well with good parental care, but, lacking this, there are numbers of diabetic children who drift out of and into hospitals, never well and never educated. For some 120 of these throughout the country, the Diabetic Association has stimulated the Ministry of Education and valuable philanthropic bodies to provide five small homes (for 20 to 30 children) where the child's diabetic state is looked after by regulated diet and insulin and from where he attends a nearby day school. Holiday camps have grown into an important activity from an early start by the Association for some 50 children in 1936. This past summer holiday camps were provided for some 300 diabetic children in Yorkshire and further south in England.

This beginning in England has encouraged the formation of similar diabetic associations all over the world. Indeed, these have now combined to form an International Diabetes Federation which pursues and stimulates not only the medical and scientific progress but also the social and economic welfare of diabetics all over the world, helping them to be good and useful citizens in spite of their diabetic condition.

Lawrence, R. D.; and Oakley, Wilfrid (*King's Coll. Hosp., London, England*): A NEW LONG-ACTING INSULIN: A PRELIMINARY TRIAL OF "LENTE" NOVO INSULIN. Brit. Medical Journal *1*:242-44, January 31, 1953.

A preliminary trial of the new Danish lente insulin supports the claim that it exerts a prolonged hypoglycemic action, lasting at least 24 hours, which is strong enough to control the blood sugar of moderately severe diabetics throughout the day without causing hypoglycemia during the night. In our experience, it has produced neither local nor general reactions and appears to be no more likely to produce hypoglycemic reactions than do the insulin preparations in use at present.

Lee, Johanna M.; and DeWitt, Stretten, Jr. (*Div. of Nutrition and Physiol., The Pub. Health Res. Inst. of the City of New York, Inc., New York, N. Y.*): STUDIES IN ALLOXAN METABOLISM. I. THE DISTRIBUTION AND EXCRETION OF INJECTED ALLOXAN. J. Biol. Chem. *197*:205-14, July 1952.

The distribution of isotope in tissues and excreta of rats and rabbits was studied following the injection of isotopic alloxan in diabetogenic doses. About two-thirds of the isotope, whether N^{15} in positions 1 and 3 or C^{14} in position 2, was found to be excreted in the urine within 3 days by the rat, mostly as an as yet unidentified material. Fecal excretion was small when compared with renal elimination. In studies with alloxan-1, 3-N^{15}, the isotope in the tissues was recovered in highest concentration in the nonprotein nitrogen fractions of the kidney, blood, lung and liver. The pancreas was relatively poor in isotope. All protein fractions were very poor in N^{15}. In several experiments in rats and in glutathine-depleted rabbits, uric acid-1, 3-N^{15} was administered, and carrier alloxan was added to solutions of the nonprotein nitrogen of the internal organs. Alloxan was reisolated, but in no case could significant concentrations of isotope be demonstrated in isolated products, which indicates the absence of significant generation of alloxan from uric acid.

Leon, Alberto P.; and Aguirre, N. (*Inst. of Pub. Health and Trop. Dis., Mexico*): BRUCELLOSIS, DIABETES AND LIVER DEFICIENCY. Am. J. Pub. Health *43*:539-41, May 1953.

The authors believe that brucellosis is a cause of diabetes and liver deficiency, and that diabetes and liver deficiency are frequent complications of brucellosis. In cases of brucellosis, they advise a careful search for diabetes and liver deficiency and in cases of diabetes and liver deficiency, a search for brucellosis.

Leon, Alberto P.; and Aguirre, Natividad (*Lab. of Bacteriology and Immunology, Inst. of Public Health and Tropical Diseases, Mexico*): BRUCELLOSIS: DIABETES AND HEPATIC INSUFFICIENCY. Revista del Instituto de Salubridad y Enfermedades Tropicales *12*:3-7, December 1951.

Among 150 cases of brucellosis caused by *Brucella Melitensis*, 101 (67.3 per cent had diabetes, while of 36 cases of other infectious diseases (syphilis, streptococcus endocarditis and amebiasis) only 5 (13.8 per cent) had hyperglycemia.

Lestradet, H. (*Paris, France*): DOES AN INCREASE IN CELLULAR GLUCOSE EXIST IN THE DIABETIC? La presse médicale *61*:466, March 28, 1953.

It is generally agreed that hyperglycemia results in an elevated level of cellular glucose and that this is widely responsible for those complications occurring in the diabetic. The author demonstrates that in the normal subject as well as in the diabetic the glucose distribution space is identical with the extracellular space. It therefore appears (1) that there is no free glucose inside the muscular cell and (2) that the free glucose is solely distributed in the extracellular medium. Therefore, it is possible to locate at the very level of the membrane the phosphorylation process that conditions the entrance of the glucose into the cell. Such data are an additional argument in favor of the concept that considers diabetes not as a disorder in the intracellular carbohydrate metabolism but merely as a hindrance in the passing of the glucose into the inside of the cell. This hindrance is compensated by the maintenance of a high concentration of glucose in the extracellular media.

Lewis, Lena A.; Page, Irvine H.; and Thomas, Christopher (*Res. Div. of the Cleveland Clin. Foundation and the Frank E. Bunts Educational Inst., Cleveland, Ohio*): EFFECT OF HEPATECTOMY ON SERUM LIPOPROTEINS IN DOGS. Am. J. Physiol. *172*:83-86, January 1953.

Hepatectomy in dogs caused no change in the plasma lipoprotein pattern as measured by ultracentrifugation for about 6 hours after operation. Later, all lipoproteins and cholesterol began to decrease in spite of hemoconcentration. Qualitatively, the lipoprotein pattern was unchanged. Concurrent studies of the electrophoretic plasma protein pattern exhibited decrease in total protein and decrease in alpha-1-globulin after 12 to 16 hours.

These results are interpreted as being due to decreased supply of these plasma components because of utilization by extrahepatic tissues and lack of hepatic synthesis.

Lipsett, Marie N.; and Moore, Frederick J. (*Dept. of Experimental Med., Univ. of Southern California Sch. of Med., and the Lab. of the Los Angeles County Hosp., Los Angeles, Calif.*): THE EFFECTS OF ADRENALECTOMY AND CORTISONE TREATMENT ON FATTY ACID OXIDIZATION BY MOUSE LIVER HOMOGENATES. J. Biol. Chem. *197*:303-08, July 1952.

Mouse liver homogenates from normal, adrenalectomized and cortisone-treated adrenalectomized animals were compared in rates of oxygen uptake, octanoate utilization and ketone body formation. The percentage of utilized octanoate which appeared as ketone bodies was markedly and significantly decreased after adrenalectomy and was restored to slightly above normal levels after cortisone therapy. The oxygen utilized per mole of octanoate disappearing was significantly reduced after adrenalectomy. It approached a value of 3. Some possible implications of these relationships with regard to the coenzyme A mechanism are discussed.

Loomis, George W. (*Univ. of Nebraska College of Med., Omaha, Neb.*): THE RENAL COMPLICATIONS OF DIABETES MELLITUS. Nebraska M. J. 37:356-59, November 1952.

The renal complications of diabetes mellitus include glycogen nephrosis, renal arteriosclerosis, intercapillary glomerulosclerosis and acute pyelonephritis. Although the evidence is equivocal, a positive attitude toward good control of the diabetes seems the only possible way to prevent or delay the renal complications. The effects of the renal complications on the diabetic state and their possible implications are discussed.

Machella, Thomas E. (*Gastro-Intestinal Sect. of Med. Clin. (Kinsey Thomas Foundation) of the Hosp. of the Univ. of Pennsylvania, Philadelphia, Pa.*): LABORATORY PROCEDURES IN THE DIAGNOSIS OF DISEASES OF THE PANCREAS. Geriatrics 1:311-21, May 1953.

Investigation of the carbohydrate metabolism may have considerable diagnostic value in diseases of the pancreas. The oral glucose tolerance test may yield a diabetic curve in patients with steatorrhea of pancreatic origin but a flat curve in patients in the active stage of sprue. Impairment of glucose utilization is detectable when sufficient islet-cell damage has occurred as a result of destruction by inflammation or carcinoma.

Martorano, J. J.; Zwemer, R. L.; and Vollmer, E. P. (*The Naval Med. Res. Inst., Bethesda, Md.*): GLUTATHIONE PROTECTION AGAINST POTASSIUM IN ADRENALECTOMIZED MICE. Am. J. Physiol. 173:1-3, April 1953.

Potassium tolerance in mice is increased by prior injection of glutathione. Evidence of adrenal cortex discharge after glutathione led to the present experiments which show that the presence of the adrenal glands is not entirely necessary to the protective effect of glutathione against potassium toxicity.

Administration of potassium chloride intraperitoneally to adrenalectomized male mice was followed by a 54 per cent survival rate in 122 mice previously treated for 3 hours with 50 mg. each of glutathione subcutaneously, as compared with a 12 per cent survival rate of 126 saline-injected controls.

Maske, H.; and Wolff, H. (*Univ. of Munich, Germany*): THE ERYTHROCYTE-ZINC CONTENT AND THE HEMOLYZING ACTION OF VARIOUS DIABETOGENIC COMPOUNDS. Acta Haematologica 9:289-301, May 1953.

A new method is described for the determination of zinc in the blood. It avoids disturbances caused by the presence of large quantities of iron.

Masri, M. S.; Lyon, I.; and Chaikoff, I. L. (*Div. of Physiol. of the Univ. of California Sch. of Med., Berkeley, Calif.*): NATURE OF THE STIMULATING ACTION OF INSULIN ON LIPOGENESIS FROM ACETATE IN FASTED RAT LIVER. J. Biol. Chem. 197:621-24, August 1952.

The action of insulin and glucose in vitro, singly and combined, upon acetate-1-C^{14} utilization for fatty acid synthesis and CO_2 formation was studied in liver slices prepared from rats fasted 18 hours. The addition of *insulin alone* to the medium had no effect on lipogenesis and CO_2 formation from the added acetate. *Glucose alone* definitely augmented the incorporation of the added C^{14} into fatty acids. The addition of *glucose plus insulin* to the medium resulted in a stimulation of lipogenesis which exceeded that observed with *glucose alone*. The authors interpret these findings to indicate that the action of insulin upon hepatic lipogenesis is secondary to its priming of glucose utilization.

Mayer, J.; Russell, Ruth E.; Bates, Margaret W.; and Dickie, Margaret M. (*Dept. of Nutrition, Harvard Sch. of Pub. Health, Boston, Mass., and Jackson Memorial Lab., Bar Harbor, Me.*): METABOLIC, NUTRITIONAL AND ENDOCRINE STUDIES OF THE HEREDITARY OBESITY-DIABETES SYNDROME OF MICE AND MECHANISM

OF ITS DEVELOPMENT. Metabolism 2:9-21, January 1953.

The obesity-diabetes syndrome of mice has been shown to be characterized by obesity, hyperglycemia, low basal metabolic rate, insulin resistance and decreased rate of oxidation of administered acetate with increased deposition as fatty acid. Further studies conducted from the metabolic, nutritional and endocrine standpoints gave the following main results: The hyperglycemia is progressive, and its onset occurs between the 9th and 10th week. The insulin resistance is considerable and can be detected both in the fasted and in the nonfasted states. The obese animals lose weight on a high-fat and a high-vitamin diet. Glucosuria disappears during the experimental period. A high-protein, carbohydrate diet checks the rapid weight increase and suppresses glucosuria without any such deterioration occurring. A glucose-free, fructose-containing diet suppresses glucosuria but does not check weight increase. Nonobese animals are not affected by these diets. Thyroxine treatment markedly increases the basal metabolic rate of the obese animals and causes them to lose weight, but it is responsible for a high mortality among these animals. The toxic effect is enhanced by the simultaneous injection of diethylstilbestrol. It was found impossible to raise the blood sugar level of the nonobese animals with growth hormone, even by prolonged treatment with large doses. By contrast, obese animals show extreme sensitivity to growth hormone, which precipitates the onset of hyperglycemia in young obese and doubles the blood sugar content of obese animals.

Mayer, Jean. ROLE OF HORMONE SECRETED BY THE ALPHA CELLS OF THE ISLANDS OF LANGERHANS ("NESOCRINE") IN THE ETIOLOGY OF THE SYNDROME "HEREDITARY OBESITY-HYPERGLYCEMIA." Comptes Rendus, Academie des Sciences 236:1604-07, April 20, 1953.

The hereditary syndrome of obesity-diabetes is characterized by the hypersecretion from the alpha cells of the islands of Langerhans of a hyperglycemic, glycogenolytic hormone, the action of which is opposed to that of insulin. The secretion of this hormone is controlled by the growth hormone. Its hypersecretion causes, by reaction, a hypersecretion of insulin, thence the decrease of granulations in the beta cells. According to the glucostatic theory of the regulation of appetite, the inhibition of the phosphorylation of glucose leads to hyperphagia. This new hormone appears, therefore, directly responsible for diabetes and indirectly responsible for obesity. Because of its multiple action upon the metabolism, it seems preferable to avoid giving it a name characterizing only one single type of action ("hyperglycemic factor," "glucagon," "anti-insulin"). Consequently, the author proposes for this hormone a name which recalls only the anatomic localization of its secretory organ. By analogy to the name of "insulin" (from the Latin insula, island), the name "nesocrine" can be derived from the Greek nesos, island.

Mercado, Teresa I. (*Lab. Tropical Diseases, Nat. Inst. of Health, Bethesda, Md.*): BLOOD SUGAR STUDIES ON THE WHITE RAT INFECTED WITH PLASMODIUM BERGHEI. Amer. J. Trop. Med. 1:932-35, November 1952 (Abstracted from Tropical Diseases Bulletin 50:383-84, May 1953).

This investigation deals with the blood sugar level of female white rats infected with plasmodium berghei. It was found that there was a marked drop in the sugar level of whole blood and serum when the parasitemia was 50 per cent or over. The value for sugar in the packed cells remained relatively constant during the infection but was higher than that found in the normal animal.

Mirand, Edwin A.; and Osborn, C. M. (*Dept. of Zoology, Syracuse Univ., Syracuse, N. Y.*): EFFECT OF FASTING ON BLOOD SUGARS IN HEREDITARY HYPOPITUITARY DWARF MICE. Proc. Soc. Exper. Biol. & Med. 81:706-08, December 1952.

The effects of fasting on the blood sugar in a strain of mice exhibiting hereditary dwarfism due to anterior pituitary deficiency were compared with normal mice similarly deprived of food. The blood sugar level of fasting dwarfs drops precipitously to a minimum of 68 mg. per cent after 96 hours. In contrast, normal mice exhibit a lesser drop, followed by some recovery, which later gives way to a minimum average of 103 mg. per cent after 96 hours of fasting. In the fasting dwarf, activity is curtailed progressively until, by the end of the fast, the dwarfs are either extremely lethargic or dead. One-third of these animals expired by the 96th hour, while the normal mice did not even appear ill. The authors conclude that the sensitiveness to fasting of the hereditary hypopituitary dwarf mice of the Bar Harbor strain is somewhat like that reported for hypophysectomized animals.

Nerenberg, S. T. (*Univ. of Minnesota, Minneapolis, Minn.*): REGRANULATION OF BETA CELLS OF ISLETS OF LANGERHANS FOLLOWING INSULIN AND STARVATION. Am. J. Clin. Path. *23*:340-42, April 1953.

Administration to rats of 4 units of protamine zinc insulin per day for 14 days or starvation for a period of time (12 days) caused the beta cells of the islets of Langerhans to lose their granules. After discontinuance of insulin therapy or starvation, the beta granules gradually reappeared. The insulin-treated animals recovered their granules on the sixth to tenth day. The starved animals recovered their granules on the third to eighth day.

If an increased amount of carbohydrate was given to insulin-treated rats, they recovered their granules earlier than on the regular diet. Prolonged insulin treatment for a period up to 3 months did not damage the beta cells. Animals on this regimen recovered their granules similarly to those treated for only 2 weeks.

Niedermeier, Siegfried: TREATMENT OF DIABETIC RETINITIS. Klinische Monatsblätter für Augenheilkunde und für augenärztliche Fortbildung *121*:559-63, 1952. (Abstr. from Am. J. Ophth. *36*:750, May 1953).

Injection of cysteine will improve other forms of hemorrhagic retinitis, but, in diabetic retinopathy, it may have a deleterious effect (5 patients). The author recommends rutin.

Nordman, J.; and Mandel, P. (*Univ. Strasbourg, Strasbourg, France*): THE METABOLISM OF GLUCIDES IN THE LENS. I. ANAEROBIC GLUCIDES. Annales d'oculistique *185*:929-43, November 1952. (Abstr. from Am. J. Ophth. *36*:558, April 1953).

Carbohydrates are apparently the most important source of energy in lens metabolism. Senile lens opacities are apparently largely due to the decreasing phosphorylization that takes place with increasing age.

Odeblad, Erik; and Enhörning, Göran (*Women's Clin., Caroline Inst., Sabbatsberg Hosp., Stockholm*): ARTERIOVENOUS GLUCOSE DIFFERENCE MEASUREMENTS ON THE RABBIT OVARY. Acta endocrinologica *13*:74-78, May 1953.

In 12 rabbits, 73 ovarian arteriovenous difference values of glucose were determined according to Folin and Wu's method. Suitable experimental and theoretical methods were developed to determine the exchange rate of glucose in mg. per min. The phases of estrogen secretory rest and estrogen secretory activity and exhaustion were produced artificially and examined. No differences were found between these functional stages. It is possible that the differences may be due to substances other than glucose.

Odom, E. T. (*Veterans Administration Hosp., Tuskegee, Ala.*): THE MANAGEMENT OF DIABETES MELLITUS IN THE AMBULATORY PATIENT. J. Nat. M. A. *45*:237-40, July 1953.

Important principles in the management of ambulatory diabetics are discussed, particularly for the benefit of the busy general practitioner.

Osnes, Martin; and Thorsen, Ragnvald K. (*Med. Dept. B, Rikshospitalet, Oslo, Norway*): CORTISONE AND CORTICOTROPIN TREATMENT IN INSULOMA. Acta medica Scandinavica *145*:44-51, March 28, 1953.

Four patients with surgically verified insulomata were treated with cortisone and corticotropin for a variable time before the surgical removal of the insuloma. Although during treatment the hypoglycemic attacks were more or less modified, the patients did not become asymptomatic until the insuloma was removed. It is recommended that treatment with cortisone and corticotropin be used only for a short time to alleviate the symptoms of hyperinsulinism when operation has to be deferred.

Park, C. R.; Brown, David H.; Cornblath, Marvin; Daughaday, William H.; and Krahl, M. E. (*Dept. of Biol. Chem., Washington Univ. Sch. of Med., St. Louis, Mo.*): THE EFFECT OF GROWTH HORMONE ON GLUCOSE UPTAKE BY THE ISOLATED RAT DIAPHRAGM. J. Biol. Chem. *197*:151-66, July 1952.

The authors found that crystalline growth hormone injected into hypophysectomized rats had a biphasic action, not only on the blood sugar but also on the glucose uptake by the diaphragm. In the first phase, there was a transient stimulation of glucose uptake associated with hypoglycemia and, in the second phase, a prolonged in-

hibition of uptake associated with relief of hypoglycemia. The stimulatory effect was found to be independent of insulin secretion and was not observed in normal rats or hypophysectomized rats pretreated with growth hormone. In the inhibitory phase, some degree of insulin resistance could be shown. The effects were obtained with microgram quantities of highly purified crystalline hormone. The authors were unable to dissociate the three activities (growth, hypoglycemia, inhibition of glucose uptake) by various physical and chemical treatments of the hormone. They conclude, therefore, that the crystalline growth hormone itself gives rise to both the stimulatory and inhibitory effects on glucose uptake. They postulate that the stimulatory action is a direct effect of the hormone as prepared, but that the inhibitory effect is indirect and depends on the modification in vivo of the crystalline protein into a directly inhibitory principle.

Patterson, John W. (*Dept. of Anat., Sch. of Med., Western Reserve Univ., Cleveland, Ohio*): EFFECT OF LOWERED BLOOD SUGAR ON DEVELOPMENT OF DIABETIC CATARACTS. Am. J. Physiol. *172*:77-82, January 1953.

A study of 60 diabetic rats demonstrated that there was an inverse relationship between the severity of the hyperglycemia and the time required for the development of cataracts. Groups of rats with blood sugars greater than 400 mg. per 100 cc. developed cataracts in approximately the same length of time. When the 33 rats with blood sugars greater than 400 mg. per 100 cc. were grouped on the basis of initial weight, the smaller animals developed cataracts more rapidly than those of greater weight. Lowering of the blood sugar by the administration of insulin completely prevented the development of cataracts and increased the growth of the rats to a normal level. Lowering of the blood sugar by the administration of phloridzin delayed or prevented the development of cataracts to the extent that the blood sugar was lowered. Phloridzin administration did not improve the growth of diabetic rats.

Patz, Arnall. (*Baltimore, Md.*): CATARACTS IN GALACTOSEMIA. Am. J. Ophth. *36*:453-62, April 1953.

The inability to metabolize galactose normally in infancy has been reported under the titles galactosemia, galactosuria or galactose diabetes. The disease is characterized by hepatomegaly, cataracts, weight loss, and high blood and urine galactose levels. Untreated, galactosemia is frequently fatal; however, on simply removing galactose from the diet, a dramatic clinical improvement occurs, with regression of cataracts, return of the liver to normal size, weight gain and termination of the galactosuria and galactosemia. A large number of cases probably go unidentified since patients die in infancy with undiagnosed hepatomegaly.

Although a specific hereditary pattern has not been demonstrated, galactosemia seems definitely to be genetically determined and indicates a familial involvement. The pathogenesis of this disease is still not clearly understood. Galactose is stored in the liver, and hepatic enlargement and dysfunction are due to fatty infiltration of the liver parenchymal cells.

A diminution of galactose intolerance was noted when glucose infusions were supplemented in patients with galactosemia. Galactose and glucose compete for the same liver enzyme system. It was found that simultaneous administration of glucose reduced the intolerance to galactose administered intravenously in patients with galactosemia. It was suggested that an associated hypoglucosemia with this disease may account for some the damaging effects of the disorder.

Picard, Jean-Louis (St. *Mary's Hosp., Tucson, Ariz.*): PHYSIOLOGY OF THE PANCREAS (Exocrine). Arizona Med. *10*:174-84, May 1953.

This article is a review of the physiology of the pancreas on an exocrine basis.

Pickard, Karl; Kelter, Joseph J.; and Rothenberg, Robert E. (*Div. of Int. Med. and Div. of Genl Surg. Cent. Med. Group of Brooklyn, Brooklyn, N. Y.*): ISLET CELL TUMOR OF THE PANCREAS WITH SURGICAL CURE. Ann. Int. Med. *38*:1306-13, June 1953.

A case of severe hyperinsulinism due to a functioning pancreatic adenoma is reported. The patient made a complete recovery following surgical removal of the adenoma. Surgical exploration is advocated in all cases of pronounced hyperinsulinism, particularly in the absence of hypopituitarism or adrenal hypocorticism.

Polglase, W. J.; Smith, Emil L.; and Tyler, Frank H. (*Lab. for the Study of Hereditary and Metabolic Dis-*

orders, and the Depts. of Biol. Chem. and Med., Univ. of Utah Coll. of Med., Salt Lake City, Utah): STUDIES ON HUMAN GLYCOGEN. I. PREPARATION, PURITY AND AVERAGE CHAIN LENGTH. J. Biol. Chem. *199*:97-104, November 1952.

Glycogen prepared from several samples of human tissue, including two cases of glycogen storage disorder, was characterized by optical rotation and by rotation of acid hydrolysates. Glycogen from human liver was found to give a more opalescent solution than rabbit liver glycogen or human muscle glycogen. A sample of glycogen from one case of glycogen storage disorder (von Gierke's) showed less turbidity in molar saline than did normal liver glycogen. By means of a periodate technic several normal human glycogen preparations from both liver and muscle tissue were observed to have about the same average chain length. Liver glycogen from a patient having glycogen storage disease primarily affecting muscle was about 25 per cent shorter in chain length than normal liver glycogen. The muscle glycogen from this patient was not definitely different in chain length from the glycogen of normal individuals. A preparation of glycogen obtained by biopsy from the liver of a patient with von Gierke's disease showed normal chain length.

Polglase, W. J. ; Brown, Douglas M.; and Smith, Emil L. (*Lab. for the Study of Hereditary and Metabolic Disorders, and the Depts. of Biol. Chem. and Med., Univ. of Utah Coll. of Med., Salt Lake City, Utah*): STUDIES ON HUMAN GLYCOGEN. II. SEDIMENTATION IN THE ULTRACENTRIFUGE. J. Biol. Chem. *199*:105-12, November 1952.

Preparations of human liver glycogen showed two distinct sedimenting peaks, indicating that the distribution of particle sizes is not continuous. These two kinds of liver glycogen were separated by chemical fractionation and by differential centrifugation in the preparative ultracentrifuge. The glycogen from a single case of liver glycogen storage disease (von Gierke's disease) contained only the lighter material. A preparation of glycogen from a case of glycogen storage disease of muscle contained a lighter fraction which was present in smaller amounts in the normal human muscle samples examined. The findings suggest to the authors that a physical difference in glycogen may occur as a result of what is considered, fundamentally, a disturbance in the enzyme system.

Queries and Minor Notes (*St. Paul, Minn.*): POSSIBLE NEUROGENIC HYPOGLYCEMIA. J.A.M.A. *151*:1463, April 18, 1953.

Treatment of this condition consists of reassurance, easing of nervous tension and the regular use of atropine or belladonna with small doses of phenobarbital. The diet should be adequate in vitamins and minerals, moderately restricted in carbohydrate (150 to 200 gm. daily), liberal in protein and adjusted in fat according to the body weight. Small forenoon, afternoon and bedtime feedings should be taken regularly; these also should be restricted in carbohydrate and liberal in protein.

Reaud, Angel (*Univ. of Havana Sch. of Med., Havana, Cuba*): DIABETES AND TUBERCULOSIS. South M. J. *46*:248-58, March 1953.

The author reports upon a study at La Esperanza Sanatorium, Havana, Cuba, during the 2.5 year period from January 1950 through May 1952. Of 3,850 patients admitted with active tuberculosis, all over 20 years of age, 38, or 0.98 per cent, had coexistent diabetes.

In contrast to the usual age incidence of diabetes in which 25 per cent of cases are under 50 years of age, in this series of 38 cases, 73.7 per cent were under 50. The ratio of males to females was 1.3 to 1 and whites to negroes 1.8 to 1. Of 2,153 male admissions, 1.11 per cent were diabetic; of 1,698 women, 0.82 per cent were diabetic. In 2,547 white patients, 1.7 per cent had diabetes; in 1,287 negro and mulatto patients, 0.62 per cent had diabetes.

Diabetes antedated tuberculosis in 71 per cent of cases; both diseases appeared simultaneously in 13.2 per cent; tuberculosis preceded diabetes in 15.8 per cent. Diabetes mellitus became manifest before the age of 40 years in 60.6 per cent of cases, the highest incidence in the group 30 to 39 years of age. Tuberculosis became manifest before the age of 40 years in 52.6 per cent of the cases, the highest incidence in the group 30 to 39 years.

In this series, on entry tuberculosis was classified as minimal in none, moderately advanced in 34.2 per cent and far advanced in 65.8 per cent. No correlation was demonstrated between history of coma, furunculosis, or gangrene and active tuberculosis. Cough, expectoration and loss of weight appeared respectively in 97, 92, and 87 per cent of cases; tubercle bacilli were readily demonstrated in 100 per cent. In this series, the

ratio of severe to moderate and mild diabetes was much higher than in nontuberculous diabetics, which supports the view that diabetes predisposes to tuberculosis.

The patients were treated with unmeasured house diets furnishing 300 C, 150 P, and 130 F, approximately 3,000 calories, and 30 of 38 exhibited remarkable improvement in nutrition. Loss of weight or failure to gain weight during treatment constituted a bad prognostic sign. PZI (protamine zinc insulin) or NPH insulin were used, supplemented with additional doses of quick-acting insulin before meals. The average daily total dose of insulin was 59 units. Clinical remissions of the tuberculosis made diabetes control much easier; during periods of reactivation or in the presence of some complication of the tuberculosis, diabetes rapidly became uncontrolled.

Therapeutic results were classified as follows: For moderately advanced disease: apparently arrested, quiescent or improved, 69.2 per cent; unimproved, 30.8 per cent. For far advanced disease: apparently arrested, quiescent or improved, 40 per cent; unimproved, 44 per cent; died, 16 per cent. During the period covered by this study, tuberculous diabetics did not have therapeutic results less favorable than recorded for comparable nondiabetics.

To promote earlier detection of tuberculosis in all diabetic patients, a chest film should be taken once a year, preferably every 6 months, and immediately if the patient begins to lose weight or his appetite deteriorates or the diabetes becomes difficult to control in a previously well-stabilized patient. Of the 38 patients in this series, only 9 (23.7 per cent) gave a history of previous contact with tuberculosis. A high index of diagnostic suspicion should be maintained to detect the infection in its early stage.

Reid, E. (*Sch. of Biochemistry, Univ. of Cambridge, England*): RELATIONSHIP OF THE DIABETOGENIC ACTIVITY OF OX PITUITARY EXTRACTS TO THEIR GROWTH HORMONE. J. Endocrin. 9:210-23, April 1953.

Different batches of crude bovine pituitary extract were compared with respect to the "D/G ratio," that is, the ratio of diabetogenic activity in cats to growth-promoting activity in rats. Purified preparations of the diabetogenic factor isolated from crude extracts appeared to consist predominantly of growth hormone (GH), as shown particularly by examination in the ultracentrifuge. The possibility that "purified GH," in common with crude extracts, might vary in D/G ratio received little support from tests performed on semi-purified GH fractions isolated from crude extracts or on purified GH preparations subjected to mildly destructive treatments, such as incubation with carboxypeptidase, which did not impair either diabetogenic or growth-promoting activity. Tests with the GH preparation (pig) of Raben and Westermeyer (1952) did not confirm their claim that it lacks diabetogenic activity. The growth-promoting activity of GH is reduced by ACTH or posterior-pituitary extract and enhanced by thyrotrophin. The diabetogenic activity of GH is known to be enhanced by ACTH under certain conditions. Variations among crude extracts in D/G ratio may thus be attributable to variations in the content of certain hormones other than GH.

Review—Mandel, E. E. (*Communicable Disease Center, Pub. Health Serv., Fed. Security Agcy., Atlanta, Ga.*): RENAL MEDULLARY NECROSIS. Am. J. Med. 13:322-27, September 1952.

Renal medullary necrosis is a serious and often fatal complication of pyelonephritis and is, therefore, most frequently encountered in patients suffering from diabetes or urinary obstructions or both. While there are no specific clinical criteria known to distinguish this secondary lesion from the underlying disease, it should be suspected in any case of progressive renal insufficiency when combined with evidence of urinary or systemic bacterial infection. A positive diagnosis in vivo can be made through examination of excreted tissue particles or of operative specimens and, at times, by means of retrograde urography.

In regard to the development of necrosis, studies of both human and experimental lesions indicate that occlusion of multiple small blood vessels, precipitated by the toxic-infectious process, plays a major role.

Prevention should be sought in the early detection and elimination of urinary infection and obstruction, particularly in the diabetic patient. Therapeutic considerations may include nephrectomy or nephrostomy, in addition to specific antibacterial medication.

Robillard, Rosario (*Saint-Luc Hosp., Montreal, Quebec, Canada*): TEMPORARY RESISTANCE TO INSULIN. L'union médicale du Canada 82:506-08, May 1953.

The administration of 11,700 units of insulin in twenty-four hours to a diabetic in severe acidosis is reported. The insulin resistance was temporary and disappeared with correction of the acidosis.

Russell, Nelson G., Jr. (*Buffalo, N. Y.*): CORONARY DISEASE IN THE SECOND CENTURY OF LIFE. Am. J. M. Sc. 225:241-44, March 1953.

The author presents clinical data and electrocardiograms of nine persons aged 100 years or more, one of whom survived a major myocardial infarction for 9 months. The group is not distinguished by a non-consumption of either tobacco or cholesterol-containing food.

Sacks, I.: HYPERMETROPIC REFRACTIVE CHANGES IN A DIABETIC. The British Journal of Ophthalmology 36: 525, September 1952 (Abstract from Am. J. Ophth. 36:740, May 1953).

The myopia and hyperopia that occur in diabetes are probably due to alterations in the refractive index of the lens brought about by osmotic changes, and they vary with changes in the diabetes. A young man is described in whom hyperopia varied as much as 3 diopters within several weeks during stabilization of his diabetes.

Sacks, Jacob (*Biol. Dept., Brookhaven Natl. Lab., Upton, N. Y.*): ALLOXAN DIABETES AND PHOSPHATE TURNOVER IN THE LIVER. Am. J. Physiol. 172:93-99, January 1953.

The author studied the effects of alloxan diabetes on the composition of the acid-soluble phosphorus of the liver and its turnover in Carworth and Sprague-Dawley rats. The principal changes found from normal were an increase of about 50 per cent in the concentration of inorganic phosphate and decreases of about one-third in the concentrations of ATP-ADP, glucose-1-phosphate, and glucose-6-phosphate. The distribution of the tracer phosphate between the bone and soft-tissue compartments was found to be the same in the diabetic animals as in the normal. In the diabetic animals the rate constants of the processes which remove tracer phosphate from the plasma were found not to differ from the normal. Indications were obtained of a lower turnover rate of the labile phosphorus of ATP-ADP and of glucose-1-phosphate in the diabetic animals. No evidence was found that might suggest a qualitative change in the operation of the phosphorylation cycle or that might account for the metabolic defect in diabetes. The changes found, both in composition of the acid-soluble phosphorus and the rate constants of the turnover, seem disproportionately small in relation to the profound alterations in carbohydrate metabolism of the diabetic state.

Schoenberger, James A.; Rix, Delores M.; Sakamoto, Arthur; Taylor, J. D.; and Kark, Robert M. (*Dept. of Med. and the Res. and Educational Hosps., Univ. of Illinois and the Dept. of Pharmacology, Abbott Labs., Chicago, Ill.*): METABOLIC EFFECTS, TOXICITY AND EXCRETION OF CALCIUM N-CYCLOHEXYLSULFAMATE (SUCARYL) IN MAN. Am. J. M. Sc. 225:551-59, May 1953.

The authors report the following results after investigating the metabolic effects, toxicity, and routes of excretion of calcium N-cyclohexylsulfamate in human subjects: (1) Ingestion by two healthy subjects of 5 gm. per day for 18 days affected only the metabolic balances for calcium and phosphorus but not for nitrogen, sodium and potassium, presumably because of the calcium content of the substance. (2) Ninety-eight and 87 per cent respectively of the ingested Sucaryl was recovered in the excreta of the two subjects. (3) Six subjects who received 5 gm. daily for 7½ months exhibited no toxic effects in the hematopoietic, cardiovascular, hepatic or renal systems. (4) All subjects developed mushy stools but no diarrhea or subjective complaints. (5) After I V administration, 70 to 90 per cent of the dose was excreted in the urine within 3 hours. Renal excretion involved both glomerular filtration and tubular secretion. (6) After repetitive oral administration, 37 per cent of the dose was excreted in the feces.

Schreier, Kurt; and Szybko, Valentine (*Children's Clin., Univ. of Heidelberg, Germany*): THE AMINO ACID METABOLISM IN DIABETES MELLITUS. Klinische Wochenschrift 31:430-34, May 1, 1953.

Microbiological studies of the amino acid metabolism in diabetics are reported. In the serum of 50 diabetics,

the amino acid level was almost always within normal limits. Only in individual cases was a tendency to high normal or slightly increased amino acid values provable. In the serum of 4 patients with diabetic coma, a distinct increase of the leucine, isoleucine, valine, phenylalanine and tyrosine values was found. Moderately increased were lysine and methionine, while the other amino acids showed no distinct increase. In normal fasting values 16 out of 100 diabetic individuals showed a stronger hyperamino-aciduria. Here, the increase in the elimination of the individual amino acids was varying. Most impressive was the increase in elimination of the cyclic amino acids and also of the leucines and of lysine. The significance of these findings is briefly discussed. An insufficient albumin synthesis due to a deficiency in energy-rich compounds is discussed as the cause of the disorder of the protein metabolism in the diabetic compensation.

Sebrell, W. H., Jr. (*U. S. Pub. Health Serv., and National Insts. of Health, Washington, D. C.*): TRENDS AND NEEDS IN NUTRITION. J.A.M.A. *152*:42-44, May 2, 1953.

Obesity is prevalent throughout the world, occurring even in countries where food is scarce and nutritional status low. In America today, it is the gravest known effect of malnutrition. Insurance records indicate that a quarter of the adult population is obese. Obesity is associated with a high mortality from cardiovascular-renal disease, diabetes childbirth and disease of the liver and gall bladder. Deaths from diabetes are more than three times as common in the obese as in persons of average weight, and deaths from cirrhosis of the liver among men are more than twice as common.

Sieker, Herbert O.; and Hickam, John B. (*Dept. of Med., Duke Univ. Sch. of Med., Durham, N. C.*): RESPONSE OF NORMAL AND DISEASED RETINAL VESSELS TO CHANGES IN BLOOD OXYGEN TENSION. Am. J. Med. *13*:652, November 1952 (Abstract of a paper presented at the Sixth Annual Meeting of the Southern Society for Clinical Research, Atlanta, Ga., January 19, 1952).

It is known that normal retinal arteries and veins will constrict when the blood-oxygen tension is increased and dilate when it is lowered. This reaction was studied in normal subjects and patients with hypertension and with diabetes by means of eye-ground photographs taken with a fundus camera while the subjects breathed air, tank oxygen and, in some cases, 5 per cent carbon dioxide or 10 per cent oxygen. The diameter of the larger vessels was measured with a low-power microscope having a scale engraved on the ocular.

The arteries of hypertensive and diabetic patients and the veins of the diabetics showed significantly less reactivity than normal vessels. Many of the diabetic patients also had hypertension, but the diabetics as a group had significantly less ($p<0.05$) arterial reactivity than the hypertensives.

The authors remark that the cause of this altered reactivity is not yet established, but its relation to vascular disease and the simplicity of the technic indicate that it deserves further study.

Silberstein, Jack S.; and Paugh, John T. (*Dept. of Internal Med., Coll. of Med., Ohio State Univ., Columbus, Ohio*): NECROTIZING RENAL PAPILLITIS. Ann. Int. Med. *38*:689-705, April 1953.

Three cases of necrotizing renal papillitis are presented from both the clinical and pathologic viewpoints. One patient, who had uncontrolled diabetes, developed septicemia, acute vegetative endocarditis and cerebral embolism. The other two patients were nondiabetics, and neither demonstrated any evidence of urinary obstruction with regard to the involved kidneys. The authors do not agree with all previous opinions suggesting that this lesion is a fulminating type of pyelonephritis. It has been emphasized by many authors that this disease, in nondiabetic subjects, is usually associated with urinary tract obstruction. The authors feel that obstruction alone does not afford an adequate explanation. They were strikingly impressed with the relative absence of significant vascular lesions in both the diabetic and the nondiabetic subjects. Antemortem diagnosis of this lesion is possible, if only one considers its possibility and is familiar with the clinical symptoms which the disease presents. With the advent of the ever-increasing number of wide-spectrum antibiotics, the authors feel that it is more important than ever to recognize and to be familiar with this condition because of the possibility of markedly lowering the mortality by controlling renal infection and preventing terminal necrotizing renal papillitis.

Steiner, Matthew M. (*Endocrine Dept., Children's Memorial Hosp., Chicago, Ill.*): RARE DWARFISM WITH

CHRONIC HYPOGLYCEMIA AND CONVULSIONS: OBSERVATIONS WITH (1) ACTH AND CORTISONE, (2) ACTH AND THYROID. J. Clin. Endocrinol. and Metab. *13*:283-99, March 1953.

The association of chronic hypoglycemia and convulsions with extreme dwarfism is reported in two siblings who showed marked sensitivity to oral thyroid. The results of therapy with ACTH and cortisone as well as with ACTH and thyroid are reported. The effect of this therapy upon blood glucose and cholesterol levels, eosinophils, weight, growth and general clinical condition is discussed. It is postulated that the unusual dwarfism of these siblings is the result of an insufficiency of the

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Stephens, John W.; and Root, Howard F. (*New England Deaconess Hosp., Boston, Mass.*): TREATMENT OF DIABETIC COMA. Postgrad. Med. *13*:164-73, February 1953.

Since 1923, the results obtained in the treatment of diabetic coma at the New England Deaconess Hospital have been reported at intervals. Recent emphasis on electrolyte balance and exchange, intracellular dehydration, the relation of glucose administration to insulin dosage, and certain vascular complications have led to this evaluation and restatement of the method employed. Clinical material consisted of 789 patients seen from 1923 through 1950. During this period, 2 series of patients were treated—the first consisting of 92 consecutive cases and the second of 49 cases—without a death. Admittedly these results were obtained because no patient appeared with such hopeless complications as carcinomatosis, fatal coronary or cerebral arterial occlusion or terminal vascular nephritis. From 1923 to 1939 the percentage of cases failing to recover was 11.9; from 1940 through 1948, 2.6 per cent failed to recover. This period included a series of 92 consecutive cases of diabetic coma treated without fatality. There has been no instance of fatality in a patient with either complicated or uncomplicated diabetic coma during the past two years.

The average dose of insulin given during the first three hours of coma therapy following admission to the hospital has risen steadily from 83 units to 253 units. It is the authors' conviction that the trend through the years toward earlier use of larger doses of insulin has been the major factor not only in the successful treatment of severe acidosis but also in the earlier diagnosis and treatment of complications that may have contributed to the onset of acidosis. The dosage of insulin in the first three hours for patients with a blood sugar value over 1,000 mg. per cent was more than 400 units; it is noted that an average of 66 units was administered before admission. This is two and a half times the amount of insulin given in a similar period when the blood sugar was below 600 mg. per cent. Because of the extreme degree of dehydration associated with the higher blood sugar values (just over 2,000 cc. of normal saline was required in the first group), greater amounts of parenteral fluid were administered—amounting to over 4,000 cc. of normal saline in the third group—when the blood sugar on admission was 1,000 mg. per cent or higher.

Sterling, Rex E.; and Longwell, Bernard B. (*Dept. of Biochemistry, Univ. of Colorado, Sch. of Med., Denver, Col.*): THE EFFECT OF ORAL AND INTRAVENOUS GLUCOSE ADMINISTRATION ON THE ADRENAL RESPONSE TO COLD EXPOSURE. Endocrinology *53*:98-105, July 1953.

The adrenal response of animals which received glucose by stomach tube before, or glucose by vein during, cold exposure was determined by measurement of adrenal cholesterol values. The effect of intravenous glucose administration at room temperature on adrenal cholesterol levels was also investigated. It was found that glucose administration at room temperature resulted in a marked decrease in adrenal cholesterol.

Striker, Cecil (*Cincinnati, Ohio*): DIABETES MELLITUS: AN ORIENTATION. Illinois M. J. *102*:235-41, October 1952.

There was a time when life was simple. We thought in terms of molecules and atoms, but now, in this atomic age, everything moves in incomprehensible speed. So it is with diabetes. Many of us can think back to the time when we thought of the diabetic in terms of the amount of sugar he had in his urine; today, this is not possible. In order to have a true understanding of diabetes, it is apparent that sugar in the urine is least important.

Tomkins, G. M.; Chaikoff, I. L.; and Bennett, L. L. (*Dept. of Physiol. of the Univ. of California, Sch. of Med., Berkeley, Calif.*): CHOLESTEROL SYNTHESIS BY LIVER. II. EFFECT OF HYPOPHYSECTOMY. J. Biol. Chem. *199*:543-45, December 1952.

The incorporation of acetate into cholesterol was compared in liver slices prepared from normal and hypophysectomized rats. Hepatic cholesterogenesis was greatly reduced in the hypophysectomized rat. Experimental evidence was presented to indicate that the depression in cholesterogenesis resulting from hypophysectomy is, in part at least, due to the loss of a hormone.

Volk, Bruno W.; and Lazarus, Sydney S. (*Div. of Laboratories, Jewish Sanitarium and Hosp. for Chronic Diseases, Brooklyn, N. Y.*): THE EFFECT OF VARYING INSULIN DOSAGES ON THE RATE OF DECLINE OF THE BLOOD SUGAR IN THE MODIFIED GLUCOSE INSULIN TOLERANCE TEST. J. Lab. & Clin. Med. *41*:684-89, May 1953.

Studies on the rate of decline of the blood sugar level calculated for the 30 to 60-minute period of the modified glucose-insulin tolerance test were carried out on ten nondiabetic individuals using the following insulin dosages: (1) 0.01 unit per kg., (2) 0.02 unit per kg., (3) 0.05 unit per kg., (4) 0.10 unit per kg., (5) 0.20 unit per kg. and (6) 0.30 unit per kg. It was found that the mean rate of decline was proportional to the insulin dosage up to 0.05 unit per kg. Further increase in insulin dosage up to 0.30 unit per kg. caused no further acceleration in the rate of decline. From these observations it is concluded that 0.1 unit per kg. is probably the most satisfactory dosage for use in the modified glucose-insulin tolerance test in the estimation of insulin sensitivity.

Walaas, E.; and Walaas, O. (*Inst. of Physiol., Univ. of Oslo, Norway*): EFFECT OF ADRENALINE AND NORADRENALINE ON CARBOHYDRATE METABOLISM OF RAT DIAPHRAGM. The Scandinavian Journal of Clinical Laboratory Investigations *4*:268-69, 1952.

Adrenaline in vitro causes glycogen breakdown, decreases glucose utilization, and increases lactic acid formation in the isolated rat diaphragm. In continued experiments it has been shown that this change in carbohydrate balance of the diaphragm is due to two different effects: 1. glycogen is broken down; 2. peripheral utilization of glucose is decreased. It was observed that l-noradrenaline as well as d,l-noradrenaline decreased glucose utilization and glycogen formation when these compounds were added to the incubation medium in vitro.

Webb, J. F.; and Isaac, G. H. (*British Military Hosp., Hong Kong*): METHOD OF ESTIMATING CEREBROSPINAL FLUID GLUCOSE. Brit. M. J. *2*:1044, November 8, 1952.

The authors discuss, in a short letter, the methods of estimation and the diagnostic value, both initially and serially, of estimation of glucose in the cerebrospinal fluid.

Wilens, Sigmund L.; and McCluskey, Robert T. (*Depts. of Pathology, Bellevue Hosp. and New York Univ. Coll. of Med., New York City*): THE COMPARATIVE FILTRATION PROPERTIES OF EXCISED ARTERIES AND VEINS. Am. J. M. Sc. *224*:540-47, Novmeber 1952.

The filtration properties of excised human iliac arteries and veins were tested with human blood serum and other fluids. Both types of vessels were found to be freely permeable to small molecular substances, such as the inorganic constituents of serum. Both were impermeable to large molecular substances, such as the cholesterol of egg-yolk solutions and India ink.

Substances of intermediate molecular size, for example, hemoglobin, serum albumin, globulin, and cholesterol, did not filter completely through both excised arteries and veins. The amount that filtered varied inversely with the molecular size of these colloidal substances. Much larger fractions were consistently found in venous rather than in arterial filtrates.

The rate of filtration of serum and other fluids through excised veins is much more rapid than through arteries. Filtration of serum through veins occurs at minimal positive pressures but does not occur through arteries at pressures of less than 20 mm. Hg.

The differences in permeability of veins and arteries to colloids is indicated by dialysis experiments. The greater retention of serum colloids within the lumen of the artery causes a higher colloidal osmotic pressure than is found in veins.

Filtration of serum lipid and other partially filterable substances through arteries results in their retention and deposition in the tissues of the artery wall. Serum lipids, however, are able to filter through the walls of veins without or with only very slight intramural deposition.

EDITORIALS

THE MAURIAC SYNDROME
Dwarfism, hepatomegaly and obesity with juvenile diabetes mellitus

A triad of symptoms of varying degrees of dwarfism, hepatomegaly and obesity, developing slowly in diabetic children, has been commonly designated the Mauriac syndrome, after P. Mauriac's first descriptions published in 1930 and 1934[1, 2]. Mauriac wrote that with the discovery of insulin a new disease was born: juvenile diabetes, with curious troubles and manifestations of endocrine disturbances not previously seen because these patients formerly did not survive. Most cases of so-called diabetic dwarfism were reported during the first fifteen years or so after insulin became available. Mauriac at first suggested that long continued administration of insulin might be responsible for the syndrome. Subsequently there has been general agreement that the syndrome develops only among "badly managed" patients and is not seen in children who from the start of their diabetes are given good diets with daily insulin dosage adequately regulated.

The various symptoms associated with retarded growth in juvenile diabetes are now usually ascribed to nutritional deficiencies, and lack of insulin, rather than to metabolic derangements peculiar to the disease itself. But further questions arise with regard to predisposing factors that may lead to the development of this syndrome in some patients more easily than in others. Conceivably, each of the three major symptoms may be determined by independent factors that accompany the diabetic trait in an individual.

The patients who display this triad of symptoms are usually described as "brittle" diabetics, hard to manage. Thus the records of poor control may be explained, if not excused, by the fact that the adjustment of insulin dosage for proper control was much more difficult in these patients than in others of the same age whose physiologic adjustments were better, under approximately similar instructions with regard to diet and insulin dosage. While the complete syndrome occurs rarely, a recent article by Darnaud and others[3] on "les formes frustes" of the Mauriac syndrome (i.e. not fully developed and with mild manifestations) suggests that these derangements may exist more often than is generally recognized but follow an abortive course if appropriate therapy is offered. Granting this possibility, the physio-pathology of separate phases of the syndrome assumes greater interest in the absence of severe manifestations.

The salient features chosen for discussion here are: *Hepatomegaly,* characterized by surcharge of the liver with fat or glycogen or both; *dwarfism,* possibly conditioned by pituitary deficiency, but with nutritional factors playing a leading role; *obesity* with moon face, possibly associated with oversecretion of corticosteroid hormones; *hypersensitivity to quick-acting insulin and favorable responses to slow-acting insulin,* possibly related to both pituitary and hepatic factors.

Joslin states that prior to the introduction of protamine zinc insulin hepatomegaly was one of the outstanding complications of juvenile diabetes. Marble and others[4] reported 60 cases in 1938, representing approximately six per cent of the juvenile diabetics coming to their clinic. All of these had records of poor control, frequent occurrence of ketosis and of hypoglycemic reactions from regular insulin with dosage poorly regulated. Following treatment with slow-acting protamine zinc insulin the liver decreased in size in 79 per cent of these cases.

Hepatomegaly in the diabetic was at first thought to be due to fatty infiltration; later, many large livers of diabetic patients have been found surcharged with glycogen, some with both glycogen and fat. Lack of insulin is the most likely primary cause of fatty infiltration, but numerous investigators suggest that it may be caused or aggravated by a deficiency of lipotropic factors. While a nutritional deficiency seemed unlikely,

when so many of the patients are obese, Freudenberg[5] made the interesting suggestion that frequent bouts of ketosis might lead to wastage of nitrogen (well known) with losses of essential amino acids such as methionine, which the body cannot synthesize, and that such losses can lead to a deficiency of the lipotropic factor choline. A number of writers claim dramatic beneficial effects from the administration of methionine, choline and inositol[3, 6]. Such results are difficult to evaluate accurately because similar results are obtained in nearly all cases merely with a good diet and correct regulation of insulin dosage to avoid the occurrence of ketosis and to avoid abrupt, wide fluctuations in blood-sugar levels with attendant reactions.

Many writers point to similarities in the symptomatology of diabetic dwarfism and glycogen storage disease (Van Creveld-Von Gierke disease), namely, dwarfism, obesity, large liver, hypersensitivity to insulin and the frequent development of ketosis. Debré[7] and others suggest the possibility that the two metabolic disorders might coexist in the same individual, and that in the large liver of the diabetic there might exist a metabolic fault of glycogen-turnover similar to that found in the glycogen storage disease. Such a possibility is made plausible by reports of the occurrence of glycogen storage disease and of diabetes mellitus in separate members of one family and by the fact that patients with glycogen storage disease have developed diabetes mellitus later in life. Although this possibility is so far not supported by chemical studies that have been done on liver glycogen or by adrenalin tolerance tests (both found normal in patients with the Mauriac syndrome) the possibility of a partial fault in liver glycogen metabolism in these diabetic patients merits further study.

The "moon face" with obesity so often noted in clinical descriptions of the diabetic dwarf suggests the possibility of excessive liberation of corticosteroid hormones by overstimulation of the adrenal glands, linked with states of poor control commonly reported in clinical histories of these patients. Such adrenal stimulation conceivably might occur during frequent episodes of hypoglycemia associated with hypersensitivity to quick-acting insulin and during periods of ketosis caused by insulin-lack, during hours when the insulin dosage was not well distributed for continuous effect. Pertinent observations on this phenomenon were reported by McArthur and others[8] from a careful metabolic study on the effects of variations in insulin dosage upon adrenal cortical activity in a nineteen-year-old diabetic male (Mongol, with diabetes of twelve-years duration). Doses of crystalline insulin that were planned to ensure normoglycemia, but entailed frequent insulin reactions, led to greatly increased corticosteroid excretion. Smaller doses of insulin, which just prevented ketonuria but allowed heavy glycosuria, had no effect on corticosteroid excretion or on eosinophil counts. On the other hand, the development of ketosis with insulin-lack is attended with increased corticosteroid excretion and fall in the eosinophil count. McArthur and co-authors[8] conclude with the comment, "—maintenance of a high concentration of adrenocortical hormones in the circulation of a diabetic patient almost certainly exerts widespread biological effects—." Perhaps the repeated adrenal stimulation of insulin reactions, even mild, alternating with periods of ketosis, which are reported frequently in the case histories of the diabetic dwarfs, may indeed have biological effects evidenced by disturbances of growth, deposition of fat, and the development of the "moon face."

Hypersensitivity to quick-acting insulin in these patients may also be associated with hepatic factors, not yet well understood. Studies done by an ingenious technic of hepatic vein catheterization led Sherlock and others[9] to classify diabetic patients as hepatic-insulin-sensitive and hepatic-insulin-insensitive. In the first group intravenous injection of insulin resulted in extremely rapid uptake of sugar from the blood, while the "insensitive" group showed a much slower uptake of sugar by the liver after the same dose of insulin. Avidity of glucose-uptake, rapid synthesis of glycogen and differences in speed of release of sugar from the liver might account for differences in tendencies of individual patients to develop hepatomegaly, with surcharge of glycogen, under uneven adjustments of insulin dosage.

Recent studies by Best and his co-workers[10, 11] on the growth-promoting action of slow-acting protamine zinc insulin in hypophysectomized rats may have an important meaning with regard to treatment of the diabetic dwarf and of milder manifestations of the metabolic derangements here grouped under the Mauriac syndrome. In hypophysectomized rats, which fail to grow and are extremely sensitive to quick-acting crystalline insulin, the administration of slow-acting protamine zinc insulin in dosage gradually increasing from 1 to 6 units per day was followed by a dramatic resumption of growth with increase in body weight, protein content and skeletal size. Best suggests that in hypophysectomized rats, a lack of insulin (ascribed to decreased liberation of endogenous insulin) may be a factor limiting growth. In the light of these new findings, it

seems probable that the beneficial effects of protamine zinc insulin in the diabetic dwarf, on which all workers agree, may be ascribed to the growth-promoting and protein anabolic action of the slow-acting insulin. Presumably, this action of the slow-acting insulin is better than that of regular insulin merely because its effects are much more gradual and more prolonged.

GEORGE M. GUEST, M.D.

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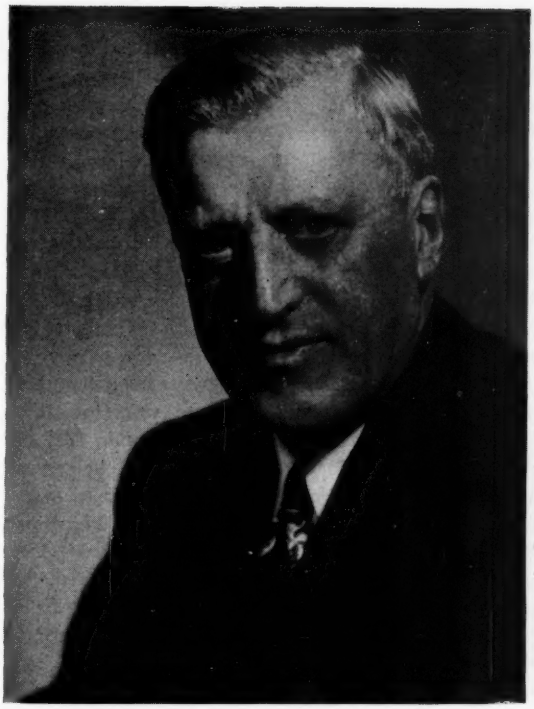
RETIREMENT OF DOCTOR WILDER

On July 1, 1953, Dr. Russell M. Wilder retired as Director of the National Institute of Arthritis and Metabolic Diseases, a position which he had held since January 1951. He was the first Director of the Institute, which is the newest of seven National Institutes of Health, and he played a leading role in the development of its resources and activities in the fields of research, support of research and training of specialists in rheumatology and metabolic diseases. Particularly, he was a leader in the formulation of the policies and program of the recently dedicated Clinical Center of the National Institutes at Bethesda, Md.



Russell M. Wilder, M.D.

Prior to accepting the post of Director of the Institute of Arthritis and Metabolic Diseases, Dr. Wilder had achieved a place of international distinction in the field of diabetes, metabolic diseases and nutrition. From 1915 to 1917, he participated with Dr. Rollin T. Woodyatt at the Presbyterian Hospital and Rush Medical College, Chicago, in important metabolic studies related to diabetes, particularly investigations of the rate of utilization of glucose and of ketone acids. He long will be remembered as one of the pioneers in the clinical use of insulin. He was the author of more than 200 scientific papers, many of them dealing with diabetes, co-author of several medical textbooks and author of two books about diabetes, *Clinical Diabetes Mellitus and Hyperinsulinism,* and *A Primer for Diabetic Patients.* In addition, he contributed much to the betterment of medical literature in the course of long service as Associate Editor of the *Archives of Internal Medicine;* he also was Associate Editor of the *American Journal of*

Medicine, the *Journal of Nutrition* and *Public Health Reports* as well as a member of the Editorial Board of DIABETES.

Dr. Wilder played an important part in the development of the activities of the American Diabetes Association. He was President of the Association in 1947. A considerable number of physicians today can trace their interest in diabetes to the inspiration of Dr. Wilder during his long period as head of the Department of Medicine and professor of medicine in the Mayo Foundation, University of Minnesota, and consulting physician on the staff of the Mayo Clinic, positions from which he retired in 1950.

Acquisition of knowledge of human nutrition has proceeded at a rapid rate in recent years, and Dr. Wilder has played a significant part in this field of scientific endeavor. For more than 20 years, he served on the Council on Foods of the American Medical Association. In 1940, he organized the Food and Nutrition Board of the National Research Council. He served as its chairman in its formative years. In 1943, he was chief of the Civilian Food Requirements Branch of the War Food Administration. Among his many contributions to the field of nutrition he perhaps will be best remembered for a key role played in bringing about widespread acceptance and use of enriched white flour and bread in the United States.

DIABETES joins Dr. Wilder's many friends in wishing him well at the climax of his distinguished career, in expressing gratitude for his contributions to diabetes and related fields and in hoping that he will find enjoyment and satisfaction in the years following his retirement.

ABSTRACTS OF MEDICAL LITERATURE

The extensive growth in the number of medical publications throughout the world has led to increasing interest in the abstracting service provided by certain medical journals. Periodicals devoted exclusively to the publication of abstracts and digests have also come to occupy an important place in medical literature. DIABETES ABSTRACTS, a forerunner of this Journal, was soon found to be invaluable by physicians interested in diabetes and related problems; the Abstracts Section of DIABETES has continued to meet the need in this field.

A new publication has now appeared to present abstracts on cancer. Issued monthly, as a section of *Excerpta Medica,* it contains abstracts in English from every available medical journal in the world. The first number in July 1953 contained 424 abstracts of papers dealing with both experimental and clinical aspects of malignancy.

Almost every phase of medical science is concerned with cancer. Medical contributions to new knowledge in regard to cancer problems are increasing rapidly. It is therefore important that those who seek to keep informed, both because of interest in research and in practice, have access to the contents of these numerous publications. This new abstract journal should, therefore, serve conveniently and effectively a large part of the medical profession.

BOOK REVIEWS

THE DIABETIC NEUROPATHIES. *By Joseph I. Goodman, M.D., Senior Clinical Instructor of the Western Reserve University, Senior Visiting Physician and Physician in Charge of Diabetic Clinic, Mt. Sinai Hospital, Medical Director Cuyahoga County Nursing Home and Cleveland Chronic Hospital, Attending Physician at Crile (Veterans Administration) Hospital, Consultant, Montefiore Home for the Aged, Cleveland, Ohio; Siegfried Baumoel, M.D., Consultant in Neurology, Mt. Sinai Hospital, Marine Hospital, Cuyahoga County Nursing Home, Polyclinic Hospital, Cleveland, Ohio; Leonard Frankel, M.D., Physician, Outpatient Department, Mt. Sinai Hospital, Cleveland, Ohio; Louis J. Marcus, M.D., Physician, Outpatient Medical Clinic, Physician assigned to Peripheral Clinic, Vascular Clinic, Mt. Sinai Hospital, Cleveland, Ohio; Sigmund Wasserman, M.D., Physician, Outpatient Department, Mt. Sinai Hospital, Cleveland, Ohio. Cloth. $4.75. Pp. 111, illustrated. Charles C. Thomas, Springfield, Ill., June 1953.*

This volume will, undoubtedly, find a place in the reference libraries. Two of the most important chapters are those devoted to symptomatology and clinical types. The authors handle these subjects in a classically didactic descriptive manner. The descriptions of the symptomatalogy are very complete. They include the sensory and motor disturbances, reflex changes, the lesions of the autonomic nervous system and the cranial nerves. The description of the neurogenic arthropathy is probably one of the highlights of the book. Every practitioner who has occasion to treat a large number of diabetic patients will encounter this syndrome and he would profit from this description. The pathology and the pathologic physiology

are discussed very adequately. The authors are, perhaps, a bit too optimistic in their statements about course and prognosis and response to treatment. The chapter relating to the pathogenesis of the diabetic neuropathies is an excellent review but the problem of the etiology remains unsolved. The bibliography is up to date and complete.

DISEASES OF THE ENDROCRINE GLANDS. *By Louis J. Soffer, M.D., Associate Attending Physician and Head of the Endrocrine Research Laboratory and Clinic, Mt. Sinai Hospital, New York, and Assistant Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons; with the assistance of J. Lester Gabrilove, M.D., Research Assistant, Endocrine Research Laboratory and Clinic, Mt. Sinai Hospital; with the section on carbohydrate metabolism, hypoglycemia and diabetes mellitus by Henry Dolger, M.D., Adjunct Physician for Metabolic Diseases, Physician in Charge of the Diabetic Clinic, Mt. Sinai Hospital; and the section on the gonads by Arthur R. Sohvil, M.D., Adjunct Physician and member of the Endocrine Research Laboratory and Clinic, Mt. Sinai Hospital. Cloth. $15.00. Pp. 1142, with illustrations. Lea and Febiger, Philadelphia, 1951.*

The book presents a comprehensive review of the entire field of endocrinology, including the embryology, anatomy, and histology of each endocrine organ, its physiologic function, the clinical manifestations of its disorders and the treatment by modern methods. Two characteristics of the book are noteworthy: first, the detailed attention given to the physiological and biochemical problems involved; second, the documentation of the numerous facts and opinions which are presented. Each chapter concludes with a long list of references.

Approximately one-eighth of the volume is devoted to diabetes. In the two chapters, dealing with the anatomy and physiology of pancreatic islet tissue, the pathogenesis of diabetes and the physiologic and metabolic derangements occurring in the disorder, Doctor Dolger has made an excellent presentation of present day knowledge. In the clinical section which follows, he departs from the traditional emphasis on dietary regulation. He devotes only about five pages to diet therapy. Only in the treatment of "mild" diabetes are positive dietary instructions presented and these are of limited nature. The menus proposed for the average adult of normal weight appear inadequate to maintain the desired normal weight.

In the section on management of diabetic coma, the dogmatic statement is made that "Glucose . . . should be used during the initial treatment of diabetic acidosis, because one-fourth of all cases of diabetic coma do not present a marked initial hyperglycemia (being under 300 mg. per cent in fact)...." It is implied that hyperglycemia may be considered advantageous in correcting ketosis; insufficient attention is given to the fact that it is an adequate supply of insulin which is actually effective. No mention is made of the risk that unusual resistance to insulin may be concealed for many hours if hyperglycemia is maintained through intravenouse infusion of glucose, or of the widely accepted custom of withholding the administration of glucose until action of the administered insulin has been demonstrated in a fall in blood sugar.

In spite of these opinions with which the reviewer cannot agree, the book can be recommended to the discriminating reader because it contains a large amount of useful information presented in readable fashion.

A TEXTBOOK OF PATHOLOGY. *By E. T. Bell, M.D., Emeritus Professor of Pathology, University of Minnesota, Minneapolis, Minn. Contributors: B. J. Clawson, M.D., Emeritus Professor of Pathology; J. S. McCartney, M.D., Professor of Pathology, University of Minnesota. 7th edition. Cloth. $12.00. Pp. 1,008 with 529 illustrations and 5 plates in color. Lea and Febiger, Philadelphia, 1952.*

This is the seventh edition of a long-popular, standard textbook of general pathology. As in the previous editions, the subject matter is presented in a very readable manner and is amply supplemented by unusually good photographs and photomicrographs which have accurate, helpful captions. The revision for this edition has been fairly thorough, so that pathologic concepts are up to date and those currently accepted. Although the bibliographies refer mostly to papers of 10 or more years ago, there are also some listings of more recent writings included in this edition.

The great interest and the numerous investigations by the author in the pathology of diabetes and other metabolic disorders, as well as in renal disease, are apparent in the presentation of written and photographic material. Such discussion includes much that is based on the author's personal opinions and observations. The section on renal disease has long been, and remains, a classic presentation of kidney pathology.

Even though some sections, such as neuropathology, are somewhat sketchy in the presentation of pathogenesis of disease processes, the book, nevertheless, should be very useful to those desiring an accurate, informative and readable reference in general pathology. The emphasis on renal and metabolic diseases will make the book valuable to the clinician interested in diabetes.

Stanley Rossiter Benedict

Creator of Laboratory Tests for Glycosuria

Herbert Pollack, M.D., New York

In 1674, Thomas Willis tasted the urine of diabetic patients to identify its sweetness. Dobson, by fermentation technics in 1715, showed this sweetness to be due to the presence of sugar. Vogel in 1815 discovered the reducing property of glucose solutions in the presence of alkaline compounds of metallic salts. It was Stanley R. Benedict about 100 years later who developed the chemical tests for sugar in the urine, which became almost universally used throughout North America. It took almost 250 years to go from tasting the urine to Benedict's tests.

In the spring of 1884 Rubner was gathering his data for the final announcement of his brilliant demonstration of the application of the law of conservation of energy to mammalian metabolism. In his laboratory at that time was an American named Wilbur O. Atwater. This same Atwater was destined to play, indirectly, a most important role in the life of a child born in Ohio at that time. Stanley R. Benedict was born in March of 1884 in Cincinnati. He was next to the youngest of six children in the Benedict household. His father was Professor of Philosophy at the University of Cincinnati. His mother was a writer and teacher. His maternal grandfather was Professor of Greek and Sanskrit at the University of Rochester. The boy Stanley grew up in an atmosphere of intellectual discussion and inquiry for the truth.

Stanley himself expressed a desire to study medicine and enrolled at the University of Cincinnati for his undergraduate work. While a student at the University, he came under the influence of Dr. J. F. Snell. Snell was a disciple of Atwater and was fresh from his laboratory, full of enthusiasm for the new developments in biochemistry and metabolism. Snell fired young Benedict's imagination and interest to the point where he gave up the idea of studying medicine. After graduation from the University of Cincinnati in 1906, with an B. A. degree, his interest was entirely in the fields of biochemistry and nutrition. Benedict then matriculated in Yale University in order to work with Russell H. Chittenden and Lafayette B. Mendel; he received a Ph.D. degree from Yale in 1908.

Mendel was at the peak of his achievement at the time that Benedict was working with him. It was in Stanley Benedict's first year at Yale that Folin introduced analytical technics of high accuracy using small samples. These analytical methods gave the clinician, for the first time, opportunities to study quantitatively the principal constituents of the blood and urine on a day-to-day basis. Benedict made a critical study of these methods and modified practically all of them. However, Benedict was especially interested in the methods for the determination of glucose in urine and blood. The problem was to find chemicals that would be reduced by glucose and not by the numerous other reducing agents present. He developed both qualitative and quantitative tests for sugar in the urine. These were recognized as superior from the standpoint of simplicity, convenience and accuracy.

Benedict was called to Syracuse University after receiving his degree from Yale. He remained for one year as an instructor. From there, he went to Columbia University where he became an associate in biochemistry. Graham Lusk, who was then building up the physiology department at Cornell University Medical College, was impressed with young Stanley Benedict. Through his influence, Benedict was invited to Cornell in 1910. He remained at Cornell until his death in 1936.

Professor Benedict taught biochemistry to the first year medical students until shortly before his death. He gave practically every lecture himself and was in

Address communications to Doctor Pollack, 70 East 77th Street, New York 21, N. Y.

and out of the student laboratory at every session. He demanded clarity, logic and above all, brevity, from the students. Long-winded circumlocutions, to evade direct answers and mask improper preparation, were usually not tried twice. A simple "unprepared" or "do not know," the students learned, would be dealt with sympathetically if not repeated too often.

In his lectures, Benedict evidenced a deep but real sense of humor. At one time in a discussion of the isolation of thyroxin, I heard him say, "I, too, isolated thyroxin and have my notes to prove it, but I knew so much about the aromatic iodide compounds that I threw the active principle down the sink and kept the residue." While he was justly proud of his achievements, he readily acknowledged an error.

No discussion of Stanley Benedict would be complete without mentioning his relationship to Otto Folin. These two men were not the bitter antagonists that many people inferred from reading the "Letters to the Editor" in the *Journal of Biological Chemistry*. They had a mutual interest in the search for truth. Criticism that was constructive was acceptable and each one was continually trying to find the flaws in the other's concepts and technics. The high esteem that Benedict held for Folin was well known by his close associates. While their discussions were almost bitter at times, Benedict almost worshipped Folin. These two men worked together in one joint effort. They were the consulting biochemists to the Metropolitan Life Insurance Company and helped organize its laboratory. Their influence was so far-reaching that it can be said that they were responsible for the present policy of the life insurance companies, to support research in the medical fields.

There was one activity of Stanley Benedict's which is not too well known. He played a most important part on the Ewing team in the early days of cancer research at the Memorial Hospital in New York City. As Chief Chemist to the Memorial Hospital, he was responsible for the development of its laboratories and the formulation of the chemical experimental work.

In addition to this full program of research and teaching, Stanley Benedict was editor of the *Journal of Biological Chemistry* from 1925 until his death. To this work he devoted a tremendous amount of time and energy. His duties as editor rarely allowed him to take a complete summer vacation to recuperate from the intense work of the school year. It can be said that this sense of responsibility to the journal hastened his death in 1936.

Few people realized that Benedict suffered from severe hypertension. His apparent withdrawal from a full social life was in part a protective mechanism to avoid as much stress as possible and to conserve his energies for the constructive work in which he was so deeply interested. Even his hobby was one which allowed him to avoid strenuous physical exercise. Benedict was a photographer of more than average ability. In line with his training, he experimented with developing solutions and reducing agents. The technical problems of photography were more exciting than the esthetic. His knowledge of optics was more than superficial as evidenced by work on the comparison colorimeters.

Stanley Benedict was a severe but just critic. He was respected by his associates and contemporaries. He was difficult to know. He was a very shy person and, because of this reticence, he was accused of being cold and distant. Those who gained his confidence knew better.

The name of Benedict is well known to physicians and diabetic patients because of his qualitative and quantitative tests for glycosuria, which have been so widely adopted. To his students, and friends in the scientific world, his memory will survive because of his substantial achievements in teaching, editing and research.

ACKNOWLEDGEMENTS

I wish to acknowledge the help received in gathering this material from Dr. Eugene DuBois, Dr. Dayton J. Edwards and Dr. Connie Guion, all of Cornell University Medical College.

A Patient Prescribes for the Physician

Fred Allen

When Fred Allen, the noted radio and television comedian, attended the banquet of the American Diabetes Association on May 30 to receive public recognition for his valuable services to the Association in promoting the welfare of diabetics, he made an after-dinner speech which long will be remembered by those present. For the benefit of readers of DIABETES who were not able to attend the banquet, Mr. Allen's speech in acceptance of the citation is presented herewith.

I certainly appreciate this rash gesture the American Diabetes Association is making. I am probably the only one at the dinner who is not an authority on the ailment. The only thing I know about diabetes is that I am fortunate enough not to have it.

As a rule honors such as this one are bestowed upon men who have made some outstanding contribution to medicine. Frankly, I have made only one worthwhile contribution to the medical profession. Down through the years I have paid all of my doctors' bills promptly. This, perhaps, should entitle me to some sort of an award.

At the moment, I realize that I am violating every rule of medical etiquette. Here am I, a patient, talking to a group of doctors and the doctors are listening. Usually, the patient, in the presence of the doctor, is permitted to list his symptoms and, when he has concluded, he is expected to listen. Before the patient can ask a question in rebuttal he finds himself in the doctor's outer office, with his bill in his hand and a nurse fluoroscoping his pockets. A patient, talking back to a doctor, is like a flounder protesting its predicament at the Fulton Fish Market.

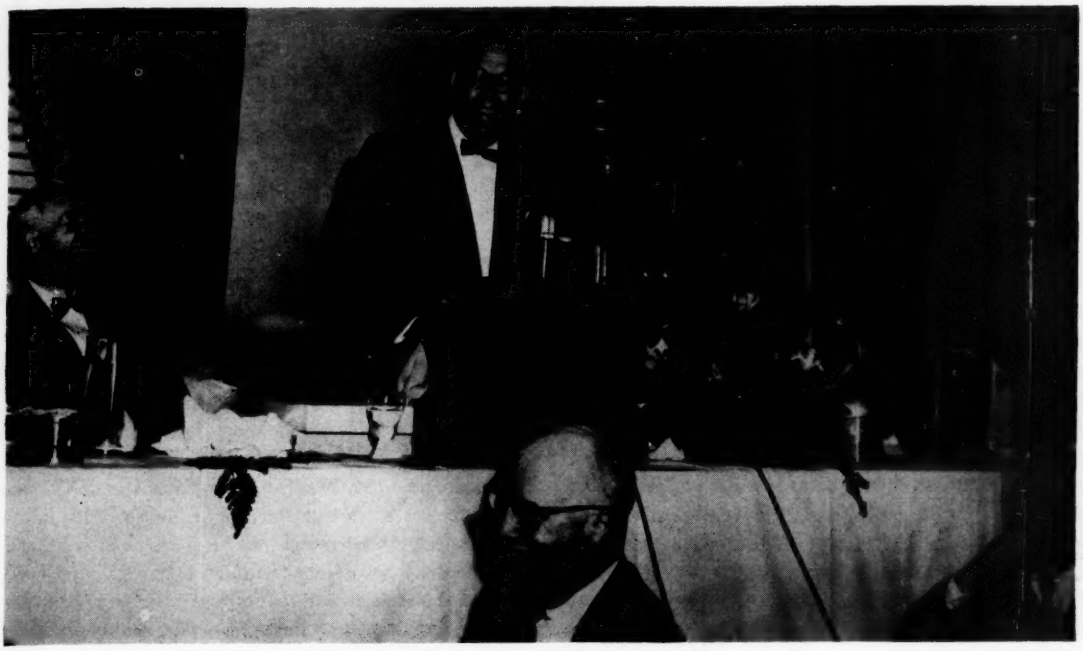
Recently, however, an unfrocked intern at a pet hospital hinted, as he was turning in his scalpel and his white shoes, that the status of the patient is in the process of changing—especially the patient who reads the daily newspapers. A doctor has been writing a series of articles that threatens to enable the subnormal patient to become his own doctor.

This doctor instructs the reader daily how he can cure hydrophobia, throbbing noises in the ears, abnormal hairiness and similar common ailments. When he gets around to explaining surgery, the newspaper reader will be able to remove his own appendix with a potato knife and a rear-view mirror.

In the past the patient was wholly dependent on his family doctor. When a baby was born, the first person it saw was the doctor. Years ago there was a subversive rumor rampant that babies were being brought by the stork. But even little children discredit it today. Recently, in one of the progressive schools during class, a small boy had his teacher locked in a closet. The teacher, not wanting to inhibit the small boy, spoke to him through the keyhole and suggested that if he was in the mood for homework he could prepare an "Essay on Mankind." The next morning the small boy brought in his essay. It read "Mankind. I asked mummy where grandma came from and mummy said the stork brought her. I asked mummy where she came from and she said the stork brought her. I asked mummy where I came from and she said the stork brought me. There have been no natural births in our family for three generations."

This small boy is a medical problem. A distinguished medical leader remarked, "A small boy who questions the stork will grow up to be a patient who doubts his doctor." There is a reason why the patient has his doubts.

In later life, the patient receives so many requests from charitable organizations asking him to help stamp out the Number One and Number Two Killers, he gets the impression that medicine depends upon survival of two things—money and research. The money he can understand. The research confuses him. He reads about doctors, in busy laboratories around the country, watching mice smoking cigarettes, to learn if a non-smoking mouse will live longer than a chain-smoking mouse. He sees pictures of guinea pigs with hypertension lying around on tiny hospital cots, having their diastoles checked every hour, to learn if high blood pressure kills more guinea pigs than medical science does. The patient hears about hundreds of hamsters locked in cubicles with telephone bells ringing in their ears incessantly. Notes are being made on the hamsters' reactions to learn if the telephone will shorten the life of a big executive if he lives like a hamster.



Members of the Association listen to Fred Allen's recommendations with appreciation.

Research, actually, is way ahead of medicine. At this very moment, in the laboratories of one pharmaceutical firm, there are three known cures for which there are no diseases.

The patient cannot understand why research, money and skill get all of the credit for the advance of medicine. He feels that the one element on which the entire profession depends never receives any recognition. In the patient's estimation the very foundation of medicine is the patient himself. What can the doctor do with his penicillin, his antibiotics and his wonder drugs if the little man with the ailment is not available to try them on?

The patient is powerless. The doctor is organized with his American Medical Association, the A.M.A. The patient, floundering around with his germ, or malady, is hopelessly outnumbered. And that is why I am here tonight. It is to warn you doctors that I am forming a patients' union to be called "The American Patients Association," the A.P.A. When the A.P.A. is organized we will demand better conditions for the patient.

The first thing we will improve is doctors' waiting rooms. These are usually drab alcoves that contain a set of nervous patients huddled together—and a few copies of some old magazines, generally the *National Geographic*. While they wait the patients upset themselves by exchanging symptoms and attempting to diagnose each other. A patient with a kidney stone opens an old *National Geographic* and reads about the rock formations in Peru. This gives him an inferiority complex. Now he not only has a kidney condition, he needs a psychiatrist. A diabetic patient looking at the sporting pages of the *National Geographic* sees a picture of two football teams playing a New Year's game at some bowl. The diabetic patient sees it is the sugar bowl and goes into shock. The atmosphere of the average doctor's waiting room is depressing.

The A.P.A. will demand that every waiting room be turned into a small night club with a television set, a bartender and a floor show going on during the doctor's office hours. While the patient is awaiting his appointment he can enjoy himself. When the doctor is ready to see him the patient will be in a rollicking mood.

The A.P.A. will take up the prescription evil. Today, the doctor gives the patient a prescription. The patient wonders what medicine he has to take. When he gets out of the office he opens the prescription and looks at the writing but he can't understand a thing. Either the doctor writes badly or the prescription is in Latin. If it is in Latin—and the patient is a Harvard man—he has no trouble. If the doctor writes badly, the patient is con-

fused, he's worried. The A.P.A. will demand that doctors write their prescriptions legibly and in words of one syllable. Then even the ignorant patient will know what concoction he is on his way to have filled.

We have some other constructive ideas—heated bedpans for hospitals in cold sections of the country, smaller pills for oboe players, with their tiny mouths, and X-ray pictures that can be framed if they come out well.

I am sure that medicine will advance, that the A.P.A. will cooperate with the A.M.A. And, as the doctor of the future, even as the doctor of the past, looks at his books at the end of his fiscal year, he will realize that things in medicine have not changed—"the patient still owes a lot to his doctor."

The Diabetes Detection Drive As a Means of Patient Education

Why does the patient with diabetes need educating? To raise this question should hardly be necessary in a gathering of clinicians interested in the problems of diabetes. Suffice it to say that adequate and continuous control of the disorder constitutes the prime requisite towards maintenance of normality of life, or the closest possible proximity thereto, and provides the only possible means in the present state of our knowledge of delaying, if not avoiding, those late complications which leave us in utter and abject helplessness.

Such constancy of control necessarily requires a patient population thoroughly informed in the fundamentals underlying the physiological processes inherent in their ailment, with a good grasp of the need of cooperation coupled with constant medical supervision. Indeed, Dr. Joslin refers pointedly to the degree of intelligence and understanding present in his group of 25-year-medal winners. Knowledge and understanding of this sort requires education by every conceivable manner or means, continuing over the patient's entire life span.

At present, such education is being provided by the physician in the course of the patient's periodic visits, by dietitians and nurses during periods of hospitalization, through literature including the ADA FORECAST, by camps for diabetic children (and why not also for adults?), and by lectures and classes sponsored in the main by Affiliates of the American Diabetes Association. Each of these provisions for educational contacts is extremely valuable and productive. Still, in spite of the steadily increasing means of contact, we find that we are reaching too few of the diabetics, a mere handful, as it were, instead of the legions that require the services. The fault of the appalling inadequacy of desirable control lies not in our failure to assume responsibility, but rather in the neglectful and lackadaisical attitudes of our patients.

The Diabetes Detection Drive, with its attendant publicity concentrating on early diagnosis and thorough treatment, can and does act in lieu of the needed thunderbolt. Certainly, it does not have the startling suddenness of the clap of thunder, nor is there inherent in our message the dread of foreboding doom, embodied in other health problems vying for public attention. Rather than such terrifying tones, it carries a theme of optimism and hope. In seeking to uncover the unrecognized diabetic, it bestirs and awakens the minds and consciousness of the known but neglectful patient. In this respect it acts rather like a goad, or a whiplash, to spur the laggards into action.

That the Detection Drive brings many neglectful patients back into our offices for re-evaluation of their status, and for subsequent supervision and treatment, thus subjecting them once more to benevolent influences, is a matter of experience, if not yet a matter of record. Up to the present, we have gathered practically no statistics on this point, but the impressions of many men in the field, convince us that the Drive exerts a beneficial effect on the education of the diabetic patient.

The Diabetes Detection Drive is capable of educating diabetic patients by stimulating the consciousness of those who have become negligent in their cooperation. Flesh tends to become inured to the goad; to keep such goad effective, the point has to be kept sharp, and the force behind it ever increasing. There are indications that the calibre of our publicity should be modified and expanded during the coming years. It might also be advisable to include a more direct approach to the diabetic patient, in addition to stressing the need of discovering the unknown diabetics.

Presented by Morris Margolin, M.D., Chairman, Diabetes Committee, Nebraska State Medical Association, before the meeting of the Committee on Diabetes and Detection at the Annual Meeting of the American Diabetes Association in New York on June 1, 1953.

Organization Section

The Fourteenth Year

Randall G. Sprague, M.D., President

As the American Diabetes Association enters its fourteenth year, it is apparent that orderly progress is being made in the development of its activities. Professional education, patient education, public education, case finding and research are the Association's major fields of endeavor. The common objective of all of these is the welfare of diabetic persons. Achievements of the Association in the past year were reviewed by the retiring president, Dr. Frank N. Allan, in his address at the 1953 annual meeting in New York. There is great promise that further progress will be achieved in this fourteenth year of the Association's history.

In the field of professional education, the scientific program of the recent annual meeting was of high quality, and the attendance by members of the Association and interested guests was greater than ever before. The Saturday afternoon joint scientific session with the Endocrine Society was again a successful occasion which helped to bring about a desirable union of interests by physicians concerned with diabetes and with general endocrinology. Since diabetes is one of the commonest endocrine diseases, a pooling of the scientific resources of the two societies at such a joint session seems to be mutually desirable.

The beginning of the fourteenth year of the Association finds DIABETES, the Journal of the American Diabetes Association, a well-established scientific publication which is carrying important information concerning diabetes and Association activities to physicians all over the world. Once again, the annual program of the Association provided much material of good scientific quality for publication in this and future issues of DIABETES. Papers of value to readers who are primarily concerned with the clinical aspects of diabetes, as well as to those who are interested in research, will continue to appear in the Journal.

The coming year will see the presentation of the second postgraduate course on diabetes and basic metabolic problems on January 18, 19 and 20, 1954, in Rochester, Minn. The great interest in the first course, which was presented last January in Toronto, makes it seem likely that an annual postgraduate course will become one of the important activities of the Association in the field of professional education.

More American physicians, and more of the American public, are now aware of the problems of diabetes than ever before. Much of the credit for this goes to the committees of local medical groups throughout the country which, in cooperation with the Association's Detection and Education Committee, have each year carried on a year-round diabetes detection drive which culminates in Diabetes Week in November. The importance of this activity lies not only in the number of new cases of diabetes which are discovered and brought under medical care, but also in the fact that it provides an unprecedented means for stimulating the interest of the medical profession and the public in the problems of diabetes. The Committee's plans for the 1953 Diabetes Detection Drive are already well advanced.

The affiliate organizations of the Association provide a powerful means for furthering the welfare of diabetic patients. Methods for promoting mutual aid and cooperation between the affiliates and the national organization are receiving careful study by a special committee of the Association. Much help was derived from a conference of representatives of affiliate associations held in New York on June 2, 1953. It is anticipated that the coming year will see further progress in reciprocal aid between the affiliates and the national association.

After several years of study by the Committee on Constitution, a new Constitution and By-Laws were adopted at the 1953 Annual Meeting. These documents provide a firm foundation for the future development of the activities of the Association and for extension of the privilege of membership to more physicians, scientists and others who are interested in the purposes of the Association.

The officers, Council and committees, as well as the personnel of the national office, are eager at all times to receive suggestions from members concerning the activities of the Association.

A Physician's Program of Service to the Public

Again this year, in the educationl phase of its program, the American Diabetes Association is emphasizing the annual Diabetes Detection Drive, opening with Diabetes Week, November 15-21. Supported by our own thirty-four Affiliate Associations and by Committees on Diabetes of State and County Medical Societies, this is a carefully planned effort to impress the public with the importance of diabetes, its early detection and the methods by which it can be controlled.

The willingness of individual physicians and organized groups to give active help in making this program a success in their communities has been highly encouraging. Year after year participation has been growing. This year some 850 committees are ready for work in the renewed campaign.

Especially to those physicians who have indicated their concern with diabetes by their membership in the Association and their subscriptions to this Journal, the American Diabetes Association looks for leadership and help in carrying this important message to the lay public. To assist them in carrying the campaign forward in their localities, the Association provides a wide variety of educational material.

For use in local newspapers, a series of news stories to be adapted by insertion of local names and details has been prepared. Along with this there is a clip sheet, containing informative articles on diabetes and feature material designed to focus attenion on the subject during the week.

Radio transcriptions are available also, for use by local stations whose cooperation can be obtained. These include a half dozen 15-minute programs of combined dramatic and educational character. There are three dramatizations—"The Lost Million," "The Story of the Russells" and "A New Leaf"—each of which drives home in story form some phase of diabetes and its care. There is a sports interview featuring Red Barber, the noted announcer, together with two diabetic athletes, Bill Nicholson, veteran outfielder, and Billy Talbert, Davis Cup tennis star. In another recorded interview, Fred Allen discusses diabetes with Talbert and with Dr. Randall G. Sprague, President of the American Diabetes Association, who himself has been a diabetic for 32 years.

Scripts of some of these programs are available also for use by stations that prefer to use local talent in presenting them. A five-minute interview for two doctors and an announcer is offered in manuscript form. Recordings of brief spot announcements by celebrities, including Fred Allen, Tallulah Bankhead, Jimmy Durante, Ethel Merman, George Sanders, Bill Cullen, Marlene Dietrich and John Henry Faulk are offered. And finally, for use on local television stations or as a "movie trailer," there is a brief film featuring the story of Billy Talbert and his diabetes.

The educational material provided includes a carefully prepared, scientifically sound series of pamphlets on diabetes and on the educational campaign. The titles indicate the contents: "Diabetes—Its Detection, Its Control;" "What Is the Diabetes Detection Drive?;" "Organizing a Successful Diabetes Detection Drive;" "Finding the Diabetic in Your Community" (10 questions asked by physicians, with answers from our Association); "Detecting Diabetes Among School Children;" "How Business and Industry Can Cooperate in the Diabetes Detection Drive;" "How Women Can Help Detect Diabetes;" "Suggested Medical Procedures and Reporting Methods for Follow-up." A campaign poster completes the series of printed matter. Because of budgetary restrictions it is impossible to send all members copies of the material but we will be glad to fili individual requests from the membership and DIABETES subscribers.

Large use is planned this year of the St. Louis Dreypak as a convenient, easily handled method of collecting specimens for urinalysis in the widespread screening tests that are a basic feature of the Detection Drive. The Association has arranged for the production of a half million of these devices and offers them for sale to local committees at cost—one cent a unit (the specimen strip, instruction sheet and envelope) or 1½ cents a unit with the three parts assembled. The Steering Committee of the Association's Committee on Detection and Education determines which requests for these shall be filled, with a view to placing them where local organization is such as to insure their being used to the best advantage.

All of this material reflects a vast amount of planning and preparation, in the light of experience in past years' campaigns, on the part of the American Diabetes Association. The actual carrying out of the campaign program—the effective utilization of this material for its purpose of public education and early detection of diabetes—depends on local physicians throughout

the country and the civic agencies they enlist to work with them in their community efforts.

This campaign, it can be assumed, does not need to be "sold" to doctors—particularly not to those who already have signified their interest in diabetes and its control. That is not the purpose of this article. Its aim is to inform the readers of DIABETES as to the content of the program and the ways in which they can help.

Every physician knows from his own experience how often diabetes goes undetected in its early stages. Numerous wholesale screening tests on large groups of people provide evidence in support of the estimate that there are in the country at least a million undetected cases of diabetes—as many as the known cases that are under medical supervision.

To seek out as many as possible of those unknown diabetics and guide them to the medical care that will enable them to live more nearly normal lives is the primary purpose of this Diabetes Detection Drive. But along with that specific, worthwhile benefit to be gained, there is the indirect value of the campaign in spreading general education in regard to diabetes. Emphasis on the theme during Diabetes Week—in the press, on radio and television—will be sufficient to produce a powerful impact on the public consciousness.

The committees promoting this effort in hundreds of communities all over the United States need the active help of all of their local physicians. For no one is in a better position to spread this educational message, full of hope for thousands of their fellow-citizens, than the doctors themselves—particularly those who already have registered their special interest in the subject of diabetes. In outlining the nation-wide program in this article, our Committee on Detection and Education does so in confidence that it will have the cooperation it needs throughout the medical profession.

JOHN A. REED, M.D., *Chairman*
Committee on Detection and Education

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DELEGATES TO THE NATIONAL HEALTH COUNCIL

Alexander Marble, Herbert Pollack, J. Richard Connelly

Second Postgraduate Course

As announced in the last issue of DIABETES, the Second Postgraduate Course of the American Diabetes Association is to be given January 18, 19 and 20, 1954, in Rochester, Minn.

The Course is under the sponsorship of the Association's Committee on Professional Education, whose chairman is Edward L. Bortz, M.D. It will be co-directed by E. H. Rynearson, M.D., and Randall G. Sprague, M.D., both of whom are Professors of Medicine, Mayo Foundation, University of Minnesota, and Consulting Physicians, Division of Medicine, Mayo Clinic, Rochester, Minn.

Association members and subscribers wishing to attend the Course are urged to register early. Last year it was necessary to return 86 applications because of limited facilities even though the registration was extended to 175. This year the maximum registration will be 125. Preference will be given to those whose applications could not be accepted last year and to members of the Association.

The registration fee for the three-day Course is $40

for members and $75 for non-members. Applications for registration should be sent to J. Richard Connelly, Executive Director, at the National Office, 11 West 42nd Street, New York 36, New York.

1954 Award for Best Paper on Diabetes by Medical Students and Interns

Members and subscribers are reminded that the Association's Council at is last meeting authorized an Award to be made in 1954 for the best paper on diabetes prepared by a medical student or by a young physician within two years after graduation from medical school.

Candidates may choose any subject related to diabetes. The paper can be a report of original studies, a biographical or historical note, a case report with suitable comment, or a review of the literature. The length may be from six to eighteen pages, typewritten with double spacing.

Those interested in submitting papers are urged to do so as early as possible. The deadline is April 1, 1954. Manuscripts should be submitted to the Editorial Office of DIABETES, 11 West 42nd Street, New York 36, N.Y. The papers will be reviewed by the Editorial Board which, in selecting the best paper, will take into consideration the value of the material and the method of presentation.

The prize of $250 is made possible once again through the generosity of the St. Louis Diabetes Association.

Scientific Sessions, Fourteenth Annual Meeting

Physicians and other scientists are invited by Henry T. Ricketts, M.D., Chairman of the Association's Committee on Scientific Programs, to submit abstracts of papers which they would like to present at the Scientific Sessions.

Persons interested are requested to submit seven copies of the abstract to facilitate review by the Committee.

Waiver of Dues for Members Entering Military Service

The Council at its last meeting voted to waive dues for members entering the Armed Forces on non-permanent status. Members wishing to ask for waiver of dues for this reason should write to John A. Reed, M.D., Secretary, at the National Office, and specify the date of entering service and the expected date of release.

New Members

The following Active Members were elected as of August 3 and September 24, 1953:

Arkansas	
Riggall, Evison R.	Prairie Grove
California	
Barry, Donald J.	Arcadia
Lyster, Russell W.	Los Angeles
O'Connor, John J.	San Francisco
Simpson, Ellen	San Francisco
Florida	
Ramsey, Russell W.	Winter Park
Georgia	
Arp, Charles R.	Atlanta
McGinty, A. Park	Atlanta
Illinois	
Bernstein, Elmer I.	Chicago
Karr, John B.	Chicago
Pok, Anton J.	Chicago
Kansas	
Luellen, Thomas J.	Wichita
Maryland	
Eastland, John S.	Baltimore
Fuller, Harvey L.	Baltimore
Harrison, Thurston	Easton
Massachusetts	
Kilgore, Philip E.	Lynn
Michigan	
Kaine, Henry D.	Ann Arbor
Meyers, Solomon G.	Detroit
Shulman, Herschel A.	Detroit
Weidner, Harold R.	Coldwater
Minnesota	
Jacobson, Wyman E.	Minneapolis
Nevada	
Taylor, Horace B.	Reno
New Jersey	
Schwartz, Samuel H.	Plainfield
New York	
Alpert, Samuel	New York
Drazin, Morris L.	New York
Falk, Sigmund	New York

Henck, Edwin A.	Scarsdale
Kent, Charles M.	Jackson Heights
Lipschutz, Paul C.	Middletown
Lynch, William G.	Glendale
Mathews, Wallace H.	Niagara Falls
Wright, Ann B.	Poughkeepsie
North Carolina	
Viau, Alberto F.	Durham
Ohio	
Chilmonczyk, Walter	Toledo
Davis, Ernest D.	Hamilton
Pennsylvania	
Polk, David S.	Rosemont
Smith, David A.	Harrisburg
Rhode Island	
Gilman, John F. W.	Providence
South Dakota	
White, Wendell W.	Faith
Tennessee	
Miller, Walter R.	Johnson City
Texas	
Allison, Farris P.	Beaumont
Doak, Edmond K.	Houston
Galt, Jabez	Dallas
Greenlee, Ralph G.	Temple
Trevino, Saul S.	San Antonio
Virginia	
Davis, Edward G., Jr.	Richmond
Hutcheson, Robert S., Jr.	Roanoke
Scherr, Edward H.	Richmond
Washington	
Steenrod, William J., Jr.	Seattle
West Virginia	
Brown, Delmer J.	Parkersburg
Jarrett, Marion F.	Charleston
Wisconsin	
Willson, Donald M.	Milwaukee

OTHER COUNTRIES

Argentina	
Camerini-Davalos, R.	Buenos Aires
Canada	
Alway, Alan E.	St. Catherines, Ont.
Smith, George W.	Toronto, Ont.
Wrenshall, Gerald A.	Toronto, Ont.
Cuba	
Garcia-Lopez, Guillermo	Havana

News of Affiliate Associations

MICHIGAN DIABETES ASSOCIATION: Amendments to the by-laws of the Association were discussed and adopted and plans were laid for lay society chapters throughout the state at a dinner meeting in the Hotel Pantlind, Grand Rapids, on September 24. Blair Holcomb, M.D., Portland, Ore. spoke on the subject "Our Responsibility to the Diabetic Patient."

NEW JERSEY DIABETES ASSOCIATION: On the afternoon of October 14 the New Jersey Diabetes Association, together with six cooperating agencies, is participating in a conference on diabetes in the Hotel Hildebrecht, Trenton. The meeting will be opened by Governor Alfred E. Driscoll. Members of the American Diabetes Association will discuss the following subjects: Hugh L. C. Wilkerson, M.D., Boston, "What We Can Learn from the Diabetes Survey in Oxford, Mass.;" Edward L. Bortz, M.D., Philadelphia, "Modern Methods of Diabetes Control;" Otto Brandman, M.D., Newark, "Pilot Study in Diabetes Screening—St. Michael's Hospital, Newark, and State Department of Health."

Deaconess Maude Behrman, Dietary Consultant to the A.D.A. FORECAST, will speak on "Highlights of Diet for Diabetics."

NORTHEASTERN NEW YORK DIABETES ASSOCIATION: Officers of the Affiliate were reelected for the coming year at a business meeting on October 1 in the Johnstown Hotel, Johnstown, N. Y. Joseph B. Cortesi, M.D., Schenectady, is President; Walter Dreyfuss, M.D., Amsterdam, Vice President; and Leonard J. Schiff, M.D., Plattsburg, Secretary-Treasurer.

PHILADELPHIA METABOLIC ASSOCIATION: Each fall the Philadelphia Metabolic Association holds an Open Forum, a custom which has proven to be highly successful. Scheduled for the evening of Monday, November 16, this year's forum will coincide with the opening

of Diabetes Week. Presentation of the newly established J. Howard Rieber award for an outstanding contribution in the field of diabetic patient education, will be made.

WISCONSIN DIABETES ASSOCIATION: A postgraduate forum on diabetes was sponsored by the Wisconsin Diabetes Association on September 19 in Marquette University School of Medicine. Members of the Association participating were William W. Engstrom, M.D., Milwaukee; F. Raymond Keating, Jr., M.D., Rochester, Minn. and Francis D. Murphy, M.D., and Bruno J. Peters, M.D., both of Milwaukee.

News Notes

International Physiological Congress

The International Physiological Congress held in Montreal, Canada, from August 31-September 4 was attended by more than 3,000 persons, with scientists present from 48 countries.

Prof. Charles H. Best served as President of the Congress. The opening plenary session was highlighted by his address of welcome in which he spoke in six different languages. During the course of the meeting, he received many eloquent tributes for his contributions to medical science and, particularly, for the part which he played in the discovery of insulin.

Doctor Best subsequently was elected President of the newly formed International Union of Physiological Societies. The latter organization was initially proposed at the Copenhagen Convention in 1950. It is a member of the International Council of Scientific Unions affiliated with the United Nations Educational, Social and Cultural Organizations and acts to coordinate the National Physiological Societies of the World.

The scientific sessions opened with a program on the metabolic influence of insulin. Chairman of the Symposium was Prof. B. A. Houssay, Buenos Aires, Argentina. Others members of the Symposium were Drs. Francis D. W. Lukens, Philadelphia; DeWitt Stetten, New York; F. G. Young, Cambridge, England; and W. C. Stadie, Philadelphia. A special program was devoted to insulin on Tuesday afternoon, September 1, under the direction of Prof. Joseph Hoet, Louvain, Belgium. The papers included: "Addition of Radioactive Amino Acids to Insulin" by Dr. H. Fraenkel-Conrat, Berkeley, Calif.; "The Nature of the Action of Insulin" by Drs. D. R. Drury and A. N. Wick, Los Angeles, Calif.; "The Effect of Insulin on the Distribution of Free Glucose in Muscle" by Drs. C. R. Park and L. N. Johnson, Nashville, Tenn.; "Effect of Insulin in Vitro upon the Contractility of the Isolated Rat Diaphragm in Potassium Deficiency" by Drs. F. G. J. Offerijns, D. Westerink and A. F. Willebrands, Amsterdam, Holland; "The Effects of Combined Adrenocortical Steroid-Growth Hormone Regimens upon the Responses to Insulin and Glucose of Hypophysectomized Dogs" by Drs. R. C. de Bodo, M. W. Sinkoff, S. P. Kiang and H. Den, New York; "A Comparison of the Insulin Extractable from the Pancreas and Islet Cell Histology in the Diabetes Mellitus of Dogs and Human Subjects" by Drs. G. A. Wrenshall, W. S. Hartroft and C. H. Best, Toronto, and "Effect of Insulin on Nitrogen Retention in the Hypophysectomized Rat" by Drs. R. T. B. Lawrence, J. M. Salter and C. H. Best, Toronto.

Of related interest were papers dealing with glucagon (the hyperglycemic-glycogenolytic factor) by Drs. A. Staub, L. Sinn and O. K. Behrens, Indianapolis; Drs. C. de Duve and C. A. Vuylsteke, Louvain, Belgium; and Drs. P. P. Foa, Harriet Weinstein, E. B. Magid, M. D. Glassman and J. A. Smith, Chicago.

Dedication of the Charles H. Best Institute

The new Charles H. Best Institute of Physiology was formally opened in Toronto, Canada, on September 15. Erected beside the Banting Institute, it will provide improved accommodations for the Department of Physiology at the University of Toronto and, in addition, it also will provide increased facilities for the work of the Banting and Best Department of Medical Research.

The dedication of the building was preceded by a special convocation at which honorary degrees were awarded to four of the distinguished visitors who were present for the occasion. These were: Dr. Detlev W. Bronk, President of The National Academy of Sciences; Dr. Elliott P. Joslin, Honorary President of the American Diabetes Association; Dr. Bernardo A. Houssay, Buenos Aires, Argentina, Nobel Laureate; and Sir Lionel Whitby, Vice Chancellor of the University of Cambridge. Other noted guests and speakers included: Sir Henry Dale, Past Presi-

dent of The Royal Society of London, Nobel Prize winner and Chairman of the Scientific Advisory Committee to the British Government during the war years; Dr. E. D. Adrian, President of The Royal Society, London; Prof. Joseph Hoet, Head of the Department of Medicine, University of Louvain, Belgium; and Dr. R. D. Lawrence, President of the International Diabetes Federation.

The Institute was formally opened by Sir Henry Dale. Lectures and informal talks given at the scientific programs proved to be of unusual interest and importance.

A complete description of the event, along with scientific papers, will appear in the January-February number of DIABETES.

Personal

The following members of the American Diabetes Association, according to an announcement from the American Heart Association, are among the recipients of the 89 research grants made for that organization's 1953-54 fiscal year: Douglas R. Drury, M.D., Los Angeles, Calif.; George W. Thorn, M.D., Boston, Mass.; Louis Tobian, Jr., M.D., Dallas, Tex.; F. Curtis Dohan, M.D., Philadelphia, Pa.; J. Russell Elkinton, M.D., Philadelphia, Pa.; T. S. Danowski, M.D., Pittsburgh, Pa.; and B. A. Houssay, M.D., Buenos Aires, Argentina.

George E. Anderson, M.D., Brooklyn, New York, on September 30 addressed the 47th Annual Meeting of the Fifth District Branch of the Medical Society of the State of New York on the subject of "Recent Advances in the Treatment of Diabetes."

Blair Holcomb, M.D., Portland, Ore., presented a paper at the Annual Session of the Michigan State Medical Society in Grand Rapids on September 24. The paper was entitled "Patients Are People—A Physician's Soliloquy."

Priscilla White, M.D., Boston, Mass., spoke before the New Jersey Academy of General Practice in Trenton on September 26. Advances made in the treatment of diabetic coma were discussed by Dr. White.

Frederick W. Williams, M.D., New York City, addressed members of the Fourth District Branch of the Medical Society of the State of New York on "Current Concepts on the Treatment of Diabetes Mellitus." The meeting was held October 1 in the Johnstown Hotel, Johnstown, N. Y.

Obituaries

HAROLD I. GRICE, M.D., a member of the American Diabetes Association since 1941, died in Ellis Hospital, Schenectady, N.Y., on April 23 after a long illness. He was 52 years old.

Doctor Grice was born in Scranton, Pa., and received his B.S. in Biology from Bucknell University in 1925 and his medical degree from Western Reserve Univer-

Following his internship at Ellis Hospital in Schenectady, Doctor Grice was appointed resident physician. While there he established a diabetes clinic and a diabetes service. He later entered private practice in Schenectady. In recent years, he had been a member of the staff of Ellis Hospital and also chief of the diabetes service.

Before coming to Ellis Hospital, he had been at New York State Hospital at Ray Brook, N. Y., and Lakeside Hospital, Cleveland, Ohio.

JOHN DAVIS PAUL, M.D., a member of the American Diabetes Association since 1944, died on February 23 at the age of 62.

A native of Philadelphia, Doctor Paul was graduated from the University of Pennsylvania Medical School in 1915, and for the next two years was a resident at Episcopal Hospital in Philadelphia. He later served at various periods as chief of the diabetes departments of Episcopal, St. Christopher's and Stetson Hospitals, all of Philadelphia. He likewise was pathologist at Misericordia Hospital, Philadelphia, from 1919 to 1924 and at St. Christopher's Hospital from 1923 to 1946. He became Medical Director of Stetson Hospital in 1944. Since 1946 he had been a staff physician at Germantown Hospital. During World War I he was a captain in the Army Medical Corps.

Doctor Paul was a member of the American Society of Clinical Pathologists and the American College of Physicians. He furthermore had been Secretary of the Philadelphia County Medical Society, a Governor of the Medical Club of Philadelphia, and a Director of the Physician's Motor Club.

JAMES J. COLLINS, M.D., Galena, Ill., a member of the American Diabetes Association since 1948, died on April 2 at the age of 47 in Dubuque, Iowa.

Doctor Collins received his B.S. from the University of Detroit and completed his medical training at Marquette University. He was a staff member of St. Joseph Mercy Hospital and Finley Hospital, Dubuque, and maintained a general practice in Galena.